120 mm

210 mm

Sevia®-*H* Tablets

(Valsartan + Hydrochlorothiazide)

DESCRIPTION:
Sevia®-*H* (Valsartan and Hydrochlorothiazide) is a combination of valsartan, an orally active, antihypertensive, specific angiotensin II receptor blocker (ARB) acting on the AT_1 receptor subtype, and hydrochlorothiazide, a diuretic

COMPOSITION:

Sevia®-*H* 80mg + 12.5mg Tablets
Each film coated tablet contains:
Valsartan USP ..... 80mg + hydrochlorothiazide BP 12.5mg

Sevia®-*H* 160mg + 25mg Tablets
Each film coated tablet contains:
Valsartan USP ..... 160mg + hydrochlorothiazide BP 25mg

CLINICAL PHARMACOLOGY:
Mechanism of Action
Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Valsartan does not inhibit ACE (also known as kininase II) which converts angiotensin I (Ang I) to angiotensin II (Ang II) and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing 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

PHARMACODYNAMICS:
Valsartan: Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80mg 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
Hydrochlorothiazide: After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours

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, since controlled clinical trials have shown a clear anti-hypertensive effect, greater than that obtained with either active substance given alone, or placebo
Valsartan
Absorption
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 (Cmax) by about 50%, although from about 8h 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
Distribution
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
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 shows multiexponential decay kinetics ($t_{½\alpha}$ <1h and $t_{½\beta}$ about 9h). 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/h and its renal clearance is 0.62 l/h (about 30% of total clearance). 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 distribution and elimination kinetics have generally been described by a 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
Excretion
Hydrochlorothiazide is eliminated predominantly as unchanged drug. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. There is more than 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

INDICATIONS:
Treatment of hypertension in adults, 18 years of age & older. Valsartan + hydrochlorothiazide fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled with monotherapy

DOSAGE AND ADMINISTRATION:
The recommended dose of valsartan+hydrochlorothiazide is once a day. When clinically appropriate either 80mg valsartan and 12.5mg hydrochlorothiazide or 160mg valsartan & 12.5mg hydrochlorothiazide or 320mg valsartan & 12.5mg hydrochlorothiazide may be used. When necessary 160mg valsartan & 25mg hydrochlorothiazide may be used. The maximum daily dose is 320mg/25mg. The maximum antihypertensive effect is seen within 2 to 4 weeks
Renal Impairment
No dosage adjustment is required for patients with mild to moderate renal impairment (Glomerular Filtration Rate(GFR)>30ml/min)
Hepatic Impairment
No dose adjustment is required for patients with mild to moderate hepatic impairment. Due to hydrochlorothiazide component, valsartan + hydrochlorothiazide fixed-dose should be used with particular caution in patients with severe hepatic impairment
Pediatric (below 18 years)
The safety and efficacy of valsartan + hydrochlorothiazide fixed-dose have not been established in children below the age of 18 years
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 recommended dose of valsartan + hydrochlorothiazide tablets, no dose adjustment is required for patients with a creatinine clearance of 30–70 ml/min. In patients with severe renal impairment (creatinine clearance <30ml/min) and patients undergoing dialysis, no data are available for valsartan + hydrochlorothiazide 160mg/25mg film-coated tablets. Valsartan is highly bound to plasma protein cannot unbind by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis 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. Hydrochlorothiazide is contraindicated in patients with severe renal impairment
Hepatic impairment
In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately 2-fold 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

OR
As directed by the physician

ADVERSE REACTIONS:
The most common reasons for discontinuation of therapy with valsartan and hydrochlorothiazide are headache and dizziness

CONTRAINDICATIONS:
Valsartan and hydrochlorothiazide is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs. Do not coadminister aliskiren with valsartan and hydrochlorothiazide in patients with diabetes

120 mm

210 mm

WARNING/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

Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance 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 valsartan + hydrochlorothiazide 160mg/25mg film-coated tablets. Sodium and/or volume depletion should be corrected before starting treatment with valsartan + hydrochlorothiazide 160mg/25mg tablets

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone system

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 has been associated with oliguria and/or progressive azotaemia, 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. The use of valsartan + hydrochlorothiazide 160mg/25mg tablets in patients with severe chronic heart failure has not been established. Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system, the application of valsartan + hydrochlorothiazide 160mg/25mg film-coated tablets as well may be associated with impairment of the renal function. Valsartan + hydrochlorothiazide 160mg/25mg tablets should not be used in these patients

Renal artery stenosis

Valsartan + hydrochlorothiazide 160mg/25mg film-coated tablets 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

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with valsartan + hydrochlorothiazide 160mg/25mg film-coated tablets as their renin-angiotensin system is not activated

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy

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

Renal impairment

No dosage adjustment is required for patients with renal impairment with a creatinine clearance ≥ 30ml/min. Periodic monitoring of serum potassium, creatinine and uric acid levels are recommended when valsartan + hydrochlorothiazide 160mg/25mg tablets is used in patients with renal impairment The concomitant use of angiotensin II receptor antagonists (AIIRAs) - including valsartan or of ACE inhibitors with aliskiren is contraindicated in patients with renal impairment (GFR < 60ml/min/1.73m^2)

Kidney transplantation

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

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, valsartan + hydrochlorothiazide 160mg/25mg tablets should be used with caution. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma

History of 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. Valsartan + hydrochlorothiazide should be immediately discontinued in patients who develop angioedema, and valsartan + hydrochlorothiazide 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, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazides diuretics. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA

Pregnancy

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

Hydrochlorothiazide

Thiazides can cross the placenta, and concentrations reached in umbilical vein approach those in the maternal plasma. Hydrochlorothiazide, like other diuretics can cause placental hypoperfusion

Nursing Mothers

It is not known whether valsartan is excreted in human milk. Valsartan is excreted into the milk of lactating rats; Hydrochlorothiazide crosses the placenta and is excreted in human breast milk. Thus it is not advisable to use Sevia®*H* in breast feeding mothers

General

Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. 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

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor antagonist (AIIRA) is therefore not recommended. The use of aliskiren in combination with valsartan + hydrochlorothiazide is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73m^2)

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

Lecithin: If a patient is hypersensitive to peanut or soya, this medicine should not be used

DRUG INTERACTIONS:

- **Antidiabetic drugs**: Dosage adjustment of antidiabetic drugs may be required
- **Cholestyramine and colestipol:** Reduced absorption of thiazides
- **Lithium:** Increased risk of lithium toxicity. Monitor serum lithium concentrations during concurrent use
- **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):** May increase risk of renal impairment. Can reduce diuretic, natriuretic and antihypertensive effects of diuretics
- **Dual inhibition of the renin-angiotensin system:** Increased risk of renal impairment, hypotension, and hyperkalemia

OVERDOSAGE:

Over dose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be I.V. infusion of normal saline solution. Valsartan cannot be eliminated by means of hemodialysis because of its strong plasma binding behavior, whereas clearance of hydrochlorothiazide will be achieved by dialysis

PRESENTATION:

Sevia®*H* 80mg/12.5mg tablets in pack of 2 x 7's
Sevia®*H* 160mg/25mg tablets in pack of 2 x 7's

STABILITY:

See expiry on the pack

INSTRUCTIONS:

Keep out of reach of children. Avoid exposure to heat, light and humidity
Store between 15 to 30ºC. Improper storage may deteriorate the medicine

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

سیویا-ایچ ٹیبلٹ

(والسارٹن+ہائیڈروکلوروتھائیزائیڈ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں

بچوں کی پہنچ سے دور رکھیں

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

P001537/S

R.N-04/HA/11/15/Pampac