120 mm

210 mm

Sevia® Tablets

(Valsartan)

DESCRIPTION:

Sevia® (valsartan) is a nonpeptide, orally active, antihypertensive and specific angiotensin II receptor blocker acting on the AT_1 receptor subtype

COMPOSITION:

Sevia®-40 40mg Tablets
Each film coated tablet contains: Valsartan USP...40mg

Sevia®-80 80mg Tablets
Each film coated tablet contains: Valsartan USP...80mg

Sevia®-160 160mg Tablets
Each film coated tablet contains: Valsartan USP...160mg

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 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

PHARMACOKINETICS:

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours with tablets and 1-2 hours with solution formulation. Mean absolute bioavailability is 23% and 39% with tablets and solution formulation, respectively. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) 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

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 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

Excretion

Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 hr. and $t_{½\beta}$ about 9 hr.). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 lit./hr. and its renal clearance is 0.62 lit./hr. (about 30% of total clearance). The half-life of valsartan is 6 hours

INDICATIONS:

- Hypertension
- Heart failure (Class II-IV)
- Post-myocardial infarction

DOSAGE AND ADMINISTRATION:

Hypertension

The recommended dose of valsartan is 80mg or 160mg once daily, irrespective of race, age, or gender. The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 320mg film-coated tablet, or a diuretic may be added. Valsartan may also be administered with other antihypertensive agents

Heart failure

The recommended starting dose of valsartan is 40mg twice daily. Uptitration to 80mg and 160mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320mg in divided doses. Evaluation of patients with heart failure should always include assessment of renal function

Post-myocardial infarction

Therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20mg twice daily, valsartan should be titrated to 40mg, 80mg, and 160mg twice daily over the next few weeks. The starting dose is provided by the 40mg divisible tablet

The target maximum dose is 160mg twice daily. In general, it is recommended that patients achieve a dose level of 80mg twice daily by two weeks after treatment initiation and that the target maximum dose, 160mg twice daily, be achieved by three months, based on the patient's tolerability. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dose reduction. Evaluation of post-myocardial infarction patients should always include assessment of renal function

Pediatric population

Use in children and adolescents

The safety and efficacy of valsartan have not been established in children and adolescents (below the age of 18 years)

Method of administration

Valsartan may be taken independently of a meal and should be administered with water

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

Impaired renal function

As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance >10ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients. Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis

Hepatic impairment

Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentrations versus degree of hepatic dysfunction. Valsartan has not been studied in patients with severe hepatic dysfunction

OR

As directed by the physician

ADVERSE REACTIONS:

The overall frequency of adverse experiences was neither dose-related nor related to gender, race, age, or regimen. The most common reasons for discontinuation of therapy with valsartan were headache and dizziness (>1%). Other adverse experiences that occurred in placebo-controlled clinical trials included viral infection (3% vs 2%), fatigue (2% vs 1%), and abdominal pain (2% vs 1%)

CONTRAINDICATIONS:

- Pregnancy category C (first trimester) and D (second and third trimesters)
- Known hypersensitivity to this product or any component of the product
- Severe hepatic or renal insufficiency
- Possible increase in serum creatinine or blood urea nitrogen in patients with unilateral or bilateral renal artery stenosis

120 mm

210 mm

WARNING / PRECAUTIONS:

Hyperkalaemia

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

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 valsartan

Sodium and/or volume depletion should be corrected before starting treatment with valsartan, for example by reducing the diuretic dose

Renal artery stenosis

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

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

Kidney transplantation

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

Primary hyperaldosteronism

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Impaired renal function

There is currently no experience on the safe use in patients with a creatinine clearance <10ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients. No dose adjustment is required for adult patients with a creatinine clearance >10ml/min. The concomitant use of AIIRAs, including valsartan, or of ACE inhibitors with aliskiren is contraindicated in patients with renal impairment (GFR < 60ml/min/1.73 m^2)

Hepatic impairment

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

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

Recent myocardial infarction

The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies. Therefore, the combination of valsartan with an ACE inhibitor is not recommended

Caution should be observed when initiating therapy in post-myocardial infarction patients. Evaluation of post-myocardial infarction patients should always include assessment of renal function

Use of valsartan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed

Heart failure

In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and valsartan has not shown any clinical benefit. This combination apparently increases the risk for adverse events and is therefore not recommended

Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function. Use of valsartan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed

In patients whose renal function may depend on the activity of the renin-angiotensin 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. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of valsartan may be associated with impairment of the renal function

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 should be immediately discontinued in patients who develop angioedema, and valsartan should not be re-administered

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

Caution is required while co-administering AIIRAs, including valsartan, with other agents blocking the RAS such as ACE inhibitors or aliskiren

Concomitant use of angiotensin II receptor antagonists (AIIRAs), including valsartan, or of ACE inhibitors with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73 m^2) is contraindicated

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

DRUG INTERACTIONS:

Dual blockage of the Renin-Angiotensin-System (RAS) with AIIRAs, ACE inhibitors, or aliskiren;

Concomitant use of angiotensin II receptor antagonists (AIIRAs), including valsartan, or of angiotensin converting enzyme (ACE) inhibitors with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73m^2) is contraindicated

Caution required with concomitant use

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

Others

In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide

OVERDOSAGE:

Symptoms

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

Treatment

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms; stabilisation of the circulatory condition is of prime importance If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken

PRESENTATION:

Sevia®-40 40mg tablets in pack of 2 x 7's
Sevia®-80 80mg tablets in pack of 2 x 7's
Sevia®-160 160mg 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 30°C. Improper storage may deteriorate the medicine

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

سیویا ٹیبلٹ

(والسارٹن)

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

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