Viostan®

Valsartan

FORMS AND PRESENTATION

Viostan® 40: Film coated tablets: Box of 30.
Viostan® 80: Film coated tablets: Box of 30.
Viostan® 160: Film coated tablets: Box of 30.
Viostan® 320: Film coated tablets: Box of 30.

COMPOSITION

Viostan® 40: Each film coated tablet contains Valsartan 40mg.
Viostan® 80: Each film coated tablet contains Valsartan 80mg.
Viostan® 160: Each film coated tablet contains Valsartan 160mg.
Viostan® 320: Each film coated tablet contains Valsartan 320mg.
Excipients: microcrystalline cellulose, crospovidone, silicon dioxide, magnesium stearate, lactose, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, red iron oxide (Viostan® 80), yellow iron oxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Agents acting on the renin-angiotensin system.
ATC code: C09CA03.
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 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.

Pharmacokinetic properties

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 (C_{max}) by about 50%, although from about 8 h 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 liters, indicating that Valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.
Biotransformation
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.
Elimination
Valsartan shows multi-exponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated by biliary excretion in feces (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 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of Valsartan is 6 hours.

INDICATIONS

Viostan® is indicated in:
- Hypertension: Treatment of essential hypertension in adults, and hypertension in children and adolescents 6 to 18 years of age.
- Recent myocardial infarction: Treatment of clinically stable adult patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction.
- Heart failure: Treatment of symptomatic heart failure in adult patients when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy.

PRECAUTIONS

- Hyperkalemia: 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. M
Monitoring of potassium should be undertaken as appropriate.
- Impaired renal function: There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/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 >10 ml/min.
- Hepatic impairment: In patients with mild to moderate hepatic impairment without cholestasis, Valsartan should be used with caution.
- 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 hemodynamics, 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 hyper-aldosteronism: Patients with primary hyper-aldosteronism 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).
- 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 azotemia 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.
- Pediatric population: Impaired renal function: Use in pediatric patients with a creatinine clearance <30 ml/min and pediatric patients undergoing dialysis has not been studied, therefore Valsartan is not recommended in these patients. No dose adjustment is required for pediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored during treatment with Valsartan. This applies particularly when Valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Impaired hepatic function: As in adults, Valsartan is contraindicated in pediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. There is limited clinical experience with Valsartan in pediatric patients with mild to moderate hepatic impairment. The dose of Valsartan should not exceed 80 mg in these patients.

Ability to drive and use machines

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

PREGNANCY AND LACTATION

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy.
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA 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.
AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, and hyperkalemia).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension.
Because no information is available regarding the use of Valsartan during breastfeeding, Valsartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

DRUG INTERACTIONS

Concomitant use not recommended
- Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. 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.
- Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels: If a medicinal product that affects potassium levels is considered necessary in combination with Valsartan, monitoring of potassium plasma levels is advised.
Caution required with concomitant use
- Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/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.

Pediatric population

In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of Valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

ADVERSE EFFECTS

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10, 000 to <1/1000); very rare (<1/10, 000), including isolated reports; not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Hypertension

- Blood and lymphatic system disorders: Decrease in hemoglobin, decrease in hematocrit, neutropenia, thrombocytopenia (not known).
- Immune system disorders: Hypersensitivity including serum sickness (not known).
- Metabolism and nutrition disorders: Increase of serum potassium, hyponatremia (not known).
- Ear and labyrinth system disorders: Vertigo (uncommon).
- Vascular disorders: Vasculitis (not known).
- Respiratory, thoracic and mediastinal disorders: Cough (uncommon).
- Gastrointestinal disorders: Abdominal pain (uncommon).
- Hepato-biliary Disorders: Elevation of liver function values including increase of serum bilirubin (not known).
- Skin and subcutaneous tissue disorders: Angioedema, rash, pruritis (not known).
- Musculoskeletal and connective tissue disorders: Myalgia (not known).
- Renal and urinary disorders: Renal failure and impairment, elevation of serum creatinine (not known).
- General disorders and administration site conditions: Fatigue (uncommon).
- pediatric population: Neurocognitive and developmental assessment of pediatric patients aged 6 to 16 years of age revealed no overall clinically relevant adverse impact after treatment with Valsartan for up to one year.

Hyperkalemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.

Post-myocardial infarction and/or heart failure (in adult patients only)

- Blood and lymphatic system disorders: Thrombocytopenia (not known).
- Immune system disorders: Hypersensitivity including serum sickness (not known).
- Metabolism and nutrition disorders: Hyperkalemia (uncommon); increase of serum potassium, hyponatremia (not known).
- Nervous system disorders: Dizziness, postural dizziness (common); syncope, headache (uncommon).
- Ear and labyrinth system disorders: Vertigo (uncommon).
- Cardiac disorders: Cardiac failure (uncommon).
- Vascular disorders: Hypotension, orthostatic hypotension (common); vasculitis (not known).
- Respiratory, thoracic and mediastinal disorders: Cough (uncommon).
- Gastrointestinal disorders: Nausea, diarrhea (uncommon).
- Hepato-biliary Disorders: Elevation of liver function values (not known).
- Skin and subcutaneous tissue disorders: Angioedema (uncommon); rash, pruritis (not known).
- Musculoskeletal and connective tissue disorders: Myalgia (not known).
- Renal and urinary disorders: Renal failure and impairment (common); acute renal failure, elevation of serum creatinine (uncommon); increase in blood urea nitrogen (not known).
- General disorders and administration site conditions: Asthenia, fatigue (uncommon).

DOSAGE AND ADMINISTRATION

Hypertension

The recommended starting dose of Viostan® is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.

Viostan® may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

Recent myocardial infarction

In clinically stable patients, therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, Viostan® should be titrated to 40 mg, 80 mg, and 160 mg twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet. The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose, 160 mg twice daily, be achieved by three months, based on the patient's tolerability. If symptomatic hypotension or renal dysfunction occur, consideration should be given to a dose reduction.

Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers, statins, and diuretics. The combination with ACE inhibitors is not recommended.

Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Heart failure

The recommended starting dose of Viostan® is 40 mg twice daily. Up-titration to 80 mg and 160 mg 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 320 mg in divided doses.

Viostan® may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and Viostan® is not recommended.

Evaluation of patients with heart failure should always include assessment of renal function.

Elderly

No dose adjustment is required in elderly patients.

Renal impairment

No dose adjustment is required for patients with a creatinine clearance > 10ml/min.

Hepatic impairment

Viostan® is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. In patients with mild to moderate hepatic impairment without cholestasis, the dose of Viostan® should not exceed 80 mg.

Pediatric hypertension

- Children and adolescents 6 to 18 years of age: The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.

Doses higher than those listed have not been studied and are therefore not recommended.

Weight	Maximum dose studied in clinical trials
≥ 18 kg to <35 kg	80 mg
≥ 35 kg to <80 kg	160 mg
≥ 80 kg to ≤160 kg	320 mg

- Children less than 6 years of age: Safety and efficacy of Viostan® in children aged 1 to 6 years have not been established.

Use in pediatric patients aged 6 to 18 years with renal impairment

Use in pediatric patients with a creatinine clearance <30 ml/min and pediatric patients undergoing dialysis has not been studied, therefore Viostan® is not recommended in these patients. No dose adjustment is required for pediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored.

Use in pediatric patients aged 6 to 18 years with hepatic impairment

As in adults, Viostan® is contraindicated in pediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. There is limited clinical experience with Viostan® in pediatric patients with mild to moderate hepatic impairment. The dose of Viostan® should not exceed 80 mg in these patients.

Pediatric heart failure and recent myocardial infarction

Viostan® is not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Method of administration

Viostan® may be taken independently of a meal and should be administered with water.

OVERDOSAGE

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

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms; stabilization 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.

Valsartan is unlikely to be removed by hemodialysis.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: September 2014.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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