Viostan® Plus

Valsartan / Hydrochlorothiazide

FORMS AND PRESENTATION

Viostan® Plus 80/12.5mg: Film coated tablets: Box of 30.
Viostan® Plus 160/12.5mg: Film coated tablets: Box of 30.
Viostan® Plus 160/25mg: Film coated tablets: Box of 30.
Viostan® Plus 320/12.5mg: Film coated tablets: Box of 30.
Viostan® Plus 320/25mg: Film coated tablets: Box of 30.

COMPOSITION

Viostan® Plus 80/12.5mg: Each film coated tablet contains Valsartan 80mg and Hydrochlorothiazide 12.5mg.
Excipients: microcrystalline cellulose, crospovidone, silica, magnesium stearate, lactose, croscarmellose sodium, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, talc, yellow iron oxide, red iron oxide.
Viostan® Plus 160/12.5mg: Each film coated tablet contains Valsartan 160mg and Hydrochlorothiazide 12.5mg.
Excipients: microcrystalline cellulose, crospovidone, silica, magnesium stearate, lactose, croscarmellose sodium, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, talc, red iron oxide.
Viostan® Plus 160/25mg: Each film coated tablet contains Valsartan 160mg and Hydrochlorothiazide 25mg.
Excipients: microcrystalline cellulose, crospovidone, silica, magnesium stearate, lactose, croscarmellose sodium, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, talc, yellow iron oxide, red iron oxide, black iron oxide.
Viostan® Plus 320/12.5mg: Each film coated tablet contains Valsartan 320mg and Hydrochlorothiazide 12.5mg.
Excipients: microcrystalline cellulose, crospovidone, silica, magnesium stearate, lactose, croscarmellose sodium, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, talc, yellow iron oxide, red iron oxide.
Viostan® Plus 320/25mg: Each film coated tablet contains Valsartan 320mg and Hydrochlorothiazide 25mg.
Excipients: microcrystalline cellulose, crospovidone, silica, magnesium stearate, lactose, croscarmellose sodium, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, talc, red iron oxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Agents acting on the rennin-angiotensin system.
ATC code: C09DA03.

Valsartan

Valsartan is an orally active 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_1receptor 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.

Hydrochlorothiazide

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na^+/Cl^- symporter perhaps by competing for the Cl^- site, thereby affecting electrolyte reabsorption mechanisms: Directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so with co-administration of Valsartan the reduction in serum potassium is less pronounced as observed under monotherapy with Hydrochlorothiazide.

Pharmacokinetic properties

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 (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 multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in feces (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 2 h), 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.
- 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.
- Elimination: 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 h.

INDICATIONS

Viosan® Plus is indicated in the treatment of essential hypertension in adults and in patients whose blood pressure is not adequately controlled on Valsartan or Hydrochlorothiazide monotherapy.

CONTRAINDICATIONS

- Hypersensitivity to Valsartan, Hydrochlorothiazide, other sulfonamide-derived medicinal products, soya oil, peanut oil or to any of the excipients.
- Second and third trimester of pregnancy.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance <30 ml/min), anuria.
- Refractory hypokalemia, hyponatremia, hypercalcemia, and symptomatic hyperuricemia.

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: Hypokalemia 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 hyponatremia and hypochloremic alkalosis. Thiazides, including Hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcemia.
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

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.
Photosensitizing actions of HCTZ could act as a possible mechanism for non-melanoma skin cancer.
Patients taking HCTZ should be informed of the risk of non-melanoma skin cancer 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 non-melanoma skin cancer.
- 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. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan/Hydrochlorothiazide.
- 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 azotemia, and in rare cases with acute renal failure. The use of Valsartan/Hydrochlorothiazide 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 as well may be associated with impairment of the renal function. Valsartan/Hydrochlorothiazide should not be used in these patients.
- Renal artery stenosis: Valsartan/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.
- Primary hyperaldosteronism: Patients with primary hyperaldosteronism should not be treated with Valsartan/Hydrochlorothiazide 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 ≥30 ml/min. Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan/Hydrochlorothiazide is used in patients with renal impairment.
- 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 should be used with caution.
- 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 hypoglycemic 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 hypercalcemia 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.
- 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.
- Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorbtion: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ability to drive and use machines

No studies on the effect of Valsartan/Hydrochlorothiazide, 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.

PREGNANCY AND LACTATION

Valsartan

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during 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 Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. 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.
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, 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.
No information is available regarding the use of Valsartan during breastfeeding.

Hydrochlorothiazide

There is limited experience with Hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of Hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women expect in rare situations where no other treatment could be used.
Hydrochlorothiazide is excreted in human milk. Therefore the use of Valsartan/Hydrochlorothiazide during breast feeding is not recommended. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

DRUG INTERACTIONS

Interactions related to both Valsartan and Hydrochlorothiazide

- Concomitant use not recommended: 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.

- Concomitant use requiring caution: Other antihypertensive agents: Valsartan/Hydrochlorothiazide may increase the effects of other agents with antihypertensive properties (e.g ACEI, beta blockers and calcium channel blockers).
Pressor amines (e.g. noradrenaline, adrenaline): Possible decreased response to pressor amines but not sufficient to preclude their use.
Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs: NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and Hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Valsartan/Hydrochlorothiazide and NSAIDs may lead to 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.

Interactions related to Valsartan

- Concomitant use not 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.
- No interaction: 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, indomethacin, Hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin could interact with the Hydrochlorothiazide component of Valsartan/Hydrochlorothiazide.

Interactions related to Hydrochlorothiazide

- Concomitant use requiring caution: Medicinal products associated with potassium loss and hypokalemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives): If these medicinal products are to be prescribed with the Valsartan/Hydrochlorothiazide combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of Hydrochlorothiazide on serum potassium.
Medicinal products that could induce torsades de pointes: Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide); Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide); some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol); others (e.g. bepridil, cisapride, diphemanil, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine i.v.). Due to the risk of hypokalemia, Hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.
Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may occur as unwanted effects favoring the onset of digitalis-induced cardiac arrhythmias.
Calcium salts and vitamin D: Administration of thiazide diuretics, including Hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.
Antidiabetic agents (oral agents and insulin): The treatment with a thiazide may influence the glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to Hydrochlorothiazide.
Beta blockers and diazoxide: Concomitant use of thiazide diuretics, including Hydrochlorothiazide, with beta blockers may increase the risk of hyperglycemia. Thiazide diuretics, including Hydrochlorothiazide, may enhance the hyperglycemic effect of diazoxide.
Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol): Dose adjustment of uricosuric medications may be necessary as Hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including Hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.
Anticholinergic agents (e.g. atropine, biperiden): The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.
Amantadine: Thiazides, including Hydrochlorothiazide, may increase the risk of adverse effects caused by amantadine.
Cholestyramine and cholestipol resins: Absorption of thiazide diuretics, including Hydrochlorothiazide, is impaired in the presence of anionic exchange resins.
Cytotoxic agents (e.g. cyclophosamide, methotrexate): Thiazides, including Hydrochlorothiazide, may reduce renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.
Non-depolarizing skeletal muscle relaxants (e.g. tubocurarine): Thiazides, including Hydrochlorothiazide, potentiate the action of curare derivatives.
Ciclosporin: Concomitant treatment with ciclosporin may increase the risk of hyperuricemia and gout-type complications.
Alcohol, anesthetics and sedatives: Potentiation of orthostatic hypotension may occur.
Methyldopa: There have been isolated reports of hemolytic anemia in patients receiving concomitant treatment with methyldopa and Hydrochlorothiazide.
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.
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.

ADVERSE EFFECTS

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

Valsartan/Hydrochlorothiazide

- Metabolism and nutrition disorders: Dehydration (uncommon).
- Nervous system disorders: Dizziness (very rare); paresthesia (uncommon); syncope (not known).
- Eye disorders: Blurred vision (uncommon).
- Ear and labyrinth disorders: Tinnitus (uncommon).
- Vascular disorders: Hypotension (uncommon).
- Respiratory, thoracic and mediastinal disorders: Cough (uncommon); non cardiogenic pulmonary edema (not known).
- Gastrointestinal disorders: Diarrhea (very rare).
- Musculoskeletal and connective tissue disorders: Myalgia (uncommon); arthralgia (very rare).
- Renal and urinary disorders: Impaired renal function (not known).
- General disorders and administration site conditions: Fatigue (uncommon).
- Investigations: Increased serum uric acid, increased serum bilirubin and serum creatinine, hypokalemia, hyponatremia, elevation of blood urea nitrogen, neutropenia (not known).

Valsartan

- Blood and lymphatic system disorders: Decrease in hemoglobin, decrease in hematocrit, thrombocytopenia (not known).
- Immune system disorders: Other hypersensitivity/allergic reactions including serum sickness (not known).
- Metabolism and nutrition disorders: Increase of serum potassium (not known).
- Ear and labyrinth disorders: Vertigo (uncommon).
- Vascular disorders: Vasculitis (not known).
- Gastrointestinal disorders: Abdominal pain (uncommon).
- Hepatobiliary disorders: Elevation of liver function values (not known).
- Skin and subcutaneous tissue disorders: Angioedema, rash, pruritus (not known).
- Renal and urinary disorders: Renal failure (not known).

Hydrochlorothiazide

- Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma) - (not known)
- Blood and lymphatic system disorders: Thrombocytopenia sometimes with purpura (rare); agranulocytosis, leucopenia, hemolytic anemia, bone marrow depression (very rare).
- Immune system disorders: Hypersenstivity reactions (very rare).
- Psychiatric disorders: Depression, sleep disturbances (rare).
- Nervous system disorders: Headache (rare).
- Cardiac disorders: Cardiac arrhythmias (rare).
- Vascular disorders: Postural hypotension (common).
- Respiratory, thoracic and mediastinal disorders: Respiratory distress including pneumonitis and pulmonary edema (very rare).
- Gastrointestinal disorders: Loss of appetite, mild nausea and vomiting (common); constipation, gastrointestinal discomfort (rare); pancreatitis (very rare).
- Hepatobiliary disorders: Intrahepatic cholestasis or jaundice (rare).
- Skin and subcutaneous tissue disorders: Urticaria and other forms of rash (common); photosensitisation (rare); necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus (very rare).
- Reproductive system and breast disorders: Impotence (common).

DOSAGE AND ADMINISTRATION

The recommended dose of Viostan® Plus 80mg/12.5mg, Viostan® Plus 160mg/12.5mg and Viostan® Plus 160mg/25mg is one film coated 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 Viostan® Plus film coated tablets 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 Viostan® Plus 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.

Method of administration

Viostan® Plus film coated tablets can be taken with or without food and should be administered with water.

Special populations

- Renal impairment: No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). Due to the Hydrochlorothiazide component, Viostan® Plus is contraindicated in patients with severe renal impairment.
- Hepatic impairment: In patients with mild to moderate hepatic impairment without cholestasis the dose of Valsartan should not exceed 80 mg. Viostan® Plus is contraindicated in patients with severe hepatic impairment.
- Elderly: No dose adjustment is required in elderly patients.
- Pediatric patients: Viostan® Plus is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

OVERDOSAGE

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, hypovolemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilization 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 hemodialysis because of its strong plasma binding behavior whereas clearance of Hydrochlorothiazide will be achieved by dialysis.

STORAGE CONDITIONS

Store below 25°C.
Keep in original pack in intact conditions.
Date of revision: June 2020.

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

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L.
Dbayeh - Lebanon