Viostan® AM Plus

Valsartan / Amlodipine / Hydrochlorothiazide

FORMS AND PRESENTATION
Viostan® AM Plus 160/5/12.5: Film Coated Tablets. Box of 30.
Viostan® AM Plus 160/10/12.5: Film Coated Tablets. Box of 30.
Viostan® AM Plus 160/5/25: Film Coated Tablets. Box of 30.
Viostan® AM Plus 160/10/25: Film Coated Tablets. Box of 30.
Viostan® AM Plus 320/10/25: Film Coated Tablets. Box of 30.

COMPOSITION
Viostan® AM Plus 160/5/12.5: Each film coated tablet contains valsartan 160mg, amlodipine besylate equivalent to amlodipine 5mg, and hydrochlorothiazide 12.5mg.
Excipients: microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol, talc, titanium dioxide.
Viostan® AM Plus 160/10/12.5: Each film coated tablet contains valsartan 160mg, amlodipine besylate equivalent to amlodipine 10mg, and hydrochlorothiazide 12.5mg.
Excipients: microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol, talc, titanium dioxide, iron oxide yellow, iron oxide red.
Viostan® AM Plus 160/5/25: Each film coated tablet contains valsartan 160mg, amlodipine besylate equivalent to amlodipine 5mg, and hydrochlorothiazide 25mg.
Excipients: microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol, talc, titanium dioxide, iron oxide yellow.
Viostan® AM Plus 160/10/25: Each film coated tablet contains valsartan 160mg, amlodipine besylate equivalent to amlodipine 10mg, and hydrochlorothiazide 25mg.
Excipients: microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol, talc, titanium dioxide, iron oxide yellow.
Viostan® AM Plus 320/10/25: Each film coated tablet contains valsartan 320mg, amlodipine besylate equivalent to amlodipine 10mg, and hydrochlorothiazide 25mg.
Excipients: microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol, talc, titanium dioxide, iron oxide yellow.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists, other combinations, ATC code: C09DX01.
Mechanism of action
Viostan® AM Plus combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: valsartan to the angiotensin II antagonist class of medicines and amlodipine belongs to the calcium antagonist class and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these substances has an additive antihypertensive effect.
Pharmacokinetic properties
Valsartan, amlodipine, and hydrochlorothiazide exhibit linear pharmacokinetics.
Valsartan/amlodipine/hydrochlorothiazide
Following oral administration of valsartan/amlodipine/ HCT in normal healthy adults, peak plasma concentrations of valsartan, amlodipine, and HCT are reached in 6 - 8 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of valsartan, amlodipine, and HCT from valsartan/amlodipine/ HCT are the same as when administered as individual dosage forms.
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.
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6 - 12 hours. Absolute bioavailability has been calculated as between 64 % and 80 %. Amlodipine bioavailability is unaffected by food ingestion.
The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 hours). 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 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.
The volume of distribution is approximately 21 l/kg. In vitro, studies with amlodipine have shown that approximately 97.5 % of circulating drug is bound to plasma proteins.
The apparent volume of distribution of hydrochlorothiazide 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.
Biotransformation
Valsartan is not transformed 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.
Amlodipine is extensively (approximately 90 %) metabolized in the liver to inactive metabolites.
Hydrochlorothiazide is eliminated predominantly as unchanged compound.
Elimination
Valsartan shows multi-exponential 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.
Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7 - 8 days. 10% of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.
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. More than 95 % of the absorbed dose is being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.
Pharmacokinetics in special populations
Elderly (age 65 years or over)
Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but this has not been shown to have any clinical significance. Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70 % in the elderly than in the young, therefore caution is required when increasing the dosage. Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers. Since the three components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended.
Renal impairment
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. Patients with mild to moderate renal impairment may therefore receive the usual initial dose. The pharmacokinetics of amlodipine are not significantly influenced by 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. Viostan® AM Plus is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis.
Hepatic impairment
On average, in patients with mild to moderate chronic liver disease, exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Due to the valsartan component, Viostan® AM Plus is contraindicated in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40 - 60 % in AUC.

INDICATIONS
Viostan® AM Plus is indicated for the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of valsartan, amlodipine, and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual component and a single-component formulation.

CONTRAINDICATIONS
- Hypersensitivity to the active substances, to other sulphonamide derivatives, to dihydropyridine derivatives, or to any of the excipients.
- Second and third trimesters of pregnancy.
- Hepatic impairment, biliary cirrhosis, or cholestasis.
- Severe renal impairment (GFR < 30 ml/min/1.73 m^2), anuria and patients undergoing dialysis.
- Concomitant use of Viostan® AM Plus with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high-grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

PRECAUTIONS
Sodium- and/or volume-depleted patients
In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur after initiation of treatment with Viostan® AM Plus. Viostan® AM Plus should be used only after correction of any pre-existing sodium and/or volume depletion.
If excessive hypotension occurs with Viostan® AM Plus, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilized.
Serum electrolyte changes
Valsartan/amlodipine/hydrochlorothiazide
Periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals to detect possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, treatment with other medicinal products or history of prior electrolyte imbalances.
Valsartan
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.
Hydrochlorothiazide
Treatment with Viostan® AM Plus should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate preexisting hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during therapy, Viostan® AM Plus should be discontinued until stable correction of the potassium balance.
Thiazide diuretics can precipitate new onset hyponatraemia and hypochloroaemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during Viostan® AM Plus therapy, the treatment should be discontinued until normalisation of natraemia.
All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.
Renal impairment
Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When Viostan® AM Plus is used in patients with renal impairment periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended. Viostan® AM Plus is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis. No dose adjustment of Viostan® AM Plus is required for patients with mild to moderate renal impairment.
Renal artery stenosis
Viostan® AM Plus should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.
Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan, and therefore, Viostan® AM Plus is not suitable in this group of patients.
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. Viostan® AM Plus should be discontinued immediately in patients who develop angioedema and should not be re-administered.
Heart failure and coronary artery disease/post-myocardial infarction
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.
Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Viostan® AM Plus (320 mg/10 mg/25 mg) since available data in these patient populations is limited.
Aortic and mitral valve stenosis
As with all other vasodilators, special caution is indicated in patients with mitral stenosis or significant aortic stenosis that is not high grade.
Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is not activated. Therefore, Viostan® AM Plus is not recommended in this population.
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

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insulin or oral hypoglycaemic agents may be required.
Due to the hydrochlorothiazide component, Viostan® AM Plus is contraindicated in symptomatic hyperuricaemia.
Thiazides reduce urinary calcium excretion and may cause intermittant and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Viostan® AM Plus is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Viostan® AM Plus should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics. If photosensitivity reaction occurs during treatment with Viostan® AM Plus, 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.
Choroidal effusion, acute myopia, and secondary acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in choroidal effusion with visual field defect, 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 a week of treatment 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 sulphonamide or penicillin allergy.
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.
Elderly (age 65 years or over)
Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of Viostan® AM Plus, 320 mg/10 mg/25 mg, since available data in this patient population are limited.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs 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 ARBs should not be used concomitantly in patients with diabetic nephropathy.
Non-melanoma skin cancer (NMSC)
Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC. Patients taking hydrochlorothiazide should be informed of the risk of NMSC 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 minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC.
Acute respiratory toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS), have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration, and hypotension. If diagnosis of ARDS is suspected, Viostan®AM Plus should be withdrawn, and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.
Effects on ability to drive and use machines
Patients taking Viostan® AM Plus and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.

PREGNANCY AND LACTATION
Pregnancy
Valsartan
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy.
Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension.
Amlodipine
Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.
Hydrochlorothiazide
Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foetoplacental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Valsartan/amlodipine/hydrochlorothiazide
Based on the existing data with the components, the use of Viostan® AM Plus is not recommended during the first trimester and contraindicated during the second and third trimester of pregnancy.
Breast-feeding
The use of Viostan® AM Plus during breast-feeding is not recommended. If Viostan® AM Plus is used during breast-feeding, doses should be kept as low as possible. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

DRUG INTERACTIONS
No drug interaction studies have been conducted with valsartan/amlodipine/HCT and other drugs, although studies have been conducted with the individual components.
Valsartan
In vitro metabolism studies have indicated that CYP450 mediated drug interaction between valsartan and co-administered drugs are unlikely because of the low extent of metabolism.
Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.
Potassium: Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.
Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy.
The antihypertensive effect of angiotensin II receptor antagonists, including valsartan may be attenuated by NSAIDs including selective COX-2 inhibitors.
Amlodipine
Simvastatin: Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.
CYP3A4 Inhibitors: Co-administration with CYP3A inhibitors (moderate and strong) result in increased systemic exposure to amlodipine warranting dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors to determine the need for dose adjustment.
CYP3A4 Inducers: Blood pressure should be monitored when amlodipine is co-administered with CYP3A4 inducers.
Hydrochlorothiazide
When administered concurrently the following drugs may interact with thiazide diuretics:
Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.
Lithium: Diuretic agents increase the risk of lithium toxicity. Monitoring of serum lithium concentrations is recommended during concurrent use.
Non-steroidal anti-inflammatory drugs (NSAIDS and COX-2 selective inhibitors): When Viostan® AM Plus and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of diuretic is obtained.
Carbamazepine: May lead to symptomatic hyponatremia.
Ion exchange resins: Staggering the dosage of hydrochlorothiazide and ion exchange resins (e.g., cholestyramine, colestipol) such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimize the interaction.
Cyclosporine: Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications.

ADVERSE EFFECTS
Adverse effects are listed below by system organ class and frequency concerning valsartan/amlodipine/HCT.
Metabolism and nutrition disorders: hypokalaemia (common); anorexia, hypercalcaemia, hyperlipidaemia, hyperuricaemia, hyponatraemia (uncommon).
Psychiatric disorders: insomnia/sleep disorders (uncommon).
Nervous system disorders: dizziness, headache (common); coordination abnormal, dizziness postural, dizziness exertional, dysgeusia, lethargy, paraesthesia, peripheral neuropathy, neuropathy, somnolence, syncope (uncommon).
Eye disorders: visual impairment (uncommon).
Ear and labyrinth disorders: vertigo (uncommon).
Cardiac disorders: tachycardia (uncommon).
Vascular disorders: hypotension (common); orthostatic hypotension, phlebitis, thrombophlebitis (uncommon).
Respiratory, thoracic, and mediastinal disorders: cough, dyspnea, throat irritation (uncommon).
Gastrointestinal disorders: dyspepsia (common); abdominal discomfort, abdominal pain upper, breath odor, diarrhea, dry mouth, nausea, vomiting (uncommon).
Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus (uncommon).
Musculoskeletal and connective tissue disorders: back pain, joint swelling, muscle spasm, muscular weakness, myalgia, pain in extremity (uncommon).
Renal and urinary disorders: pollakiuria (common); blood creatinine increased, acute renal failure (uncommon).
Reproductive system and breast disorders: impotence (uncommon).
General disorders and administration site conditions: fatigue, oedema (common); abasia, gait disturbance, asthenia, discomfort, malaise, non-cardiac chest pain (uncommon).

DOSAGE AND ADMINISTRATION
Posology
The recommended dose of Viostan® AM Plus is one tablet per day, to be taken preferably in the morning. Before switching to Viostan® AM Plus, patients should be controlled on stable doses of the monocomponents taken at the same time. The dose of Viostan® AM Plus should be based on the doses of the individual components of the combination at the time of switching.
The maximum recommended dose of Viostan® AM Plus is 320 mg/10 mg/25 mg.
Special populations
Renal impairment
Due to the hydrochlorothiazide component, Viostan® AM Plus is contraindicated for use in patients with anuria and in patients with severe renal impairment.
No adjustment of the initial dose is required for patients with mild to moderate renal impairment.
Hepatic impairment
Viostan® AM Plus is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan and therefore Viostan® AM Plus is not suitable in this group of patients. When switching eligible hypertensive patients with hepatic impairment to Viostan® AM Plus, the lowest available dose of the amlodipine component should be used.
Heart failure and coronary artery disease
Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Viostan® AM Plus 320 mg/10 mg/25 mg.
Elderly (age 65 years or over)
Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of Viostan® AM Plus, 320 mg/10 mg/25 mg. When switching eligible elderly hypertensive patients to Viostan® AM Plus, the lowest available dose of the amlodipine component should be used.
Method of administration
Oral use.
Viostan® AM Plus can be taken with or without food.
The tablets should be swallowed whole with some water, at the same time of the day and preferably in the morning.

OVERDOSAGE
Symptoms
The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension, including shock with fatal outcome, have been reported with amlodipine.
Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.
Treatment
Valsartan/Amlodipine/Hydrochlorothiazide
Clinically significant hypotension due to valsartan/amlodipine/HCT overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure if there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

STORAGE CONDITIONS
Store below 30ºC.
Keep in original pack in intact conditions.

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Manufacturer and Marketing Authorization Holder
Benta S.A.L. - Lebanon