Viostan® AM

Valsartan / Amlodipine Besylate

FORMS AND PRESENTATION
Viostan® AM 160/5; Film coated tablets; box of 30.
Viostan® AM 160/10; Film coated tablets; box of 30.

COMPOSITION
Viostan® AM 160/5: Each film coated tablet contains 160mg of Valsartan and 5mg of Amlodipine (as Amlodipine Besylate).
Viostan® AM 160/10: Each film coated tablet contains 160mg of Valsartan and 10mg of Amlodipine (as Amlodipine Besylate).
Excipients: Microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol, talc, titanium dioxide, yellow iron oxide, red iron oxide (Viostan® AM 160/10).

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers.
ATC code: C09DB01
Viostan® AM combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.
Amlodipine/Valsartan
The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours.
Pharmacokinetic properties
Linearity
Amlodipine and valsartan exhibit linear pharmacokinetics.
Amlodipine/Valsartan
Following oral administration of Viostan® AM, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively. The rate and extent of absorption of Viostan® AM are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets.
Amlodipine
Absorption: 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.
Distribution: 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.
Biotransformation: Amlodipine is extensively (approximately 90%) metabolized in the liver to inactive metabolites.
Elimination: 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. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.
Valsartan
Absorption: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%, although from about 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 litres, 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 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.
Elimination: Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

INDICATIONS
Treatment of essential hypertension.
Viostan® AM is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

CONTRAINDICATIONS
- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Concomitant use of Viostan® AM with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m²).
- Second and third trimesters of pregnancy.
- 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
The safety and efficacy of amlodipine in hypertensive crisis have not been established.
Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during 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.
Sodium- and/or volume-depleted patients
Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Viostan® AM in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of Viostan® AM or close medical supervision at the start of treatment is recommended.
If hypotension occurs with Viostan® AM, 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.
Hyperkalaemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.
Renal artery stenosis
Viostan® AM 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.
Kidney transplantation
To date there is no experience of the safe use of Viostan® AM in patients who have had a recent kidney transplantation.
Hepatic impairment
Valsartan is mostly eliminated unchanged via the bile. The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering Viostan® AM to patients with mild to moderate hepatic impairment or biliary obstructive disorders.
In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.
Renal impairment
No dosage adjustment of Viostan® AM is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m²). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.
Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease.
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 medicinal products, including ACE inhibitors. Viostan® AM should be discontinued immediately in patients who develop angioedema and should not be re-administered.
Heart failure/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.
Aortic and mitral valve stenosis
As with all other vasodilators, special caution is indicated in patients suffering from mitral stenosis or significant aortic stenosis that is not high grade.
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.
Viostan® AM has not been studied in any patient population other than hypertension.
Effects on ability to drive and use machines
Patients taking Viostan® AM and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.
Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
Amlodipine
The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. 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.
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.
Breast-feeding
Amlodipine is excreted in human milk . The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3–7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. No information is available regarding the use of Viostan® AM during breast-feeding, therefore Viostan®AM is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
Fertility
There are no clinical studies on fertility with Viostan® AM.
Valsartan
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).
Amlodipine
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

DRUG INTERACTIONS
Interactions common to the combination
No drug-drug interaction studies have been performed with Viostan® AM and other medicinal

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products.

To be taken into account with concomitant use

Other antihypertensive agents

Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination.

Interactions linked to amlodipine

Concomitant use not recommended

Grapefruit or grapefruit juice

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Caution required with concomitant use

CYP3A4 inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Simvastatin

Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

To be taken into account with concomitant use

Others

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

Interactions linked to valsartan

Concomitant use not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diurectic is also used, the risk of lithium toxicity may presumably be increased further with Viostan® AM.

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 to be prescribed 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.

Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)

The results of an in vitro study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren

Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Others

In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

ADVERSE EFFECTS

Summary of the safety profile

The following adverse reactions were found to be the most frequently occurring or the most significant or severe: nasopharyngitis, influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush.

list of adverse reactions

Adverse reactions have been ranked under headings of frequency 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).

Common

- Nasopharyngitis, Influenza
- Hypokalaemia
- Headache
- Asthenia, Fatigue, Facial oedema, Flushing/hot flush, Oedema, Oedema peripheral, Pitting oedema

Uncommon

- Anorexia, Hypercalcaemia, Hyperlipidaemia, Hyperuricaemia, Hyponatraemia
- Coordination abnormal, Dizziness, Dizziness postural, Paraesthesia, Somnolence
- Visual impairment
- Vertigo
- Palpitations, Tachycardia
- Othostatic hypotension
- Cough, Pharyngolaryngeal pain
- Abdominal discomfort, abdominal pain upper, Constipation, Diarrhoea, Dry mouth, Nausea
- Erythema, Rash
- Arthralgia, Back pain, Joint swelling

Rare

- Hypersensitivity
- Anxiety
- Visual disturbance
- Tinnitus
- Syncope
- Hypotension
- Exanthema, Hyperhidrosis, Pruritus
- Muscle spasm, Sensation of heaviness
- Pollakiuria, Polyuria
- Erectile dysfunction

DOSAGE AND ADMINISTRATION

Posology

The recommended dose of Viostan® AM is one tablet per day.

Viostan® AM 160/5 may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or valsartan 160 mg alone.

Viostan® AM 160/10 may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10 mg or valsartan 160 mg alone or with Viostan® AM 160/5.

Viostan® AM can be used with or without food.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

For convenience, patients receiving valsartan and amlodipine from separate tablets/capsules may be switched to Viostan® AM containing the same component doses.

Renal impairment

There are no available clinical data in severely renally impaired patients. No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Hepatic impairment

Viostan® AM is contraindicated in patients with severe hepatic impairment.

Caution should be exercised when administering Viostan® AM to patients with hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients with hepatic impairment to amlodipine or Viostan® AM, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Elderly (age 65 years or over)

In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients to amlodipine or Viostan® AM, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

Paediatric population

The safety and efficacy of Viostan® AM in children aged below 18 years have not been established. No data are available.

Method of administration

Oral use.

It is recommended to take Viostan® AM with some water.

OVERDOSAGE

Symptoms

There is no experience of overdose with Viostan® AM. 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 up to and including shock with fatal outcome have been reported.

Treatment

If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Viostan® AM 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, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of Revision: November 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

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