

PERINDOPRIL ARGININE + AMLODIPINE BESILATE

VIACORAM® INITIO

3.5 mg/2.5 mg Tablet
Antihypertensive

DESCRIPTION:

Viacoram Initio 3.5 mg/2.5 mg: White, round tablet, 5 mm diameter.
Viacoram 7 mg/5 mg: White, round tablet, 6 mm diameter, engraved with  on one face.

FORMULATION:

Viacoram Initio 3.5 mg/2.5 mg: Each tablet contains 2.378 mg perindopril equivalent to 3.5 mg perindopril arginine and 3.4675 mg amlodipine besilate equivalent to 2.5 mg amlodipine. Excipient with known effect: 31.62 mg lactose monohydrate.
Viacoram 7 mg/5 mg: Each tablet contains 4.756 mg perindopril equivalent to 7 mg perindopril arginine and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine. Excipient with known effect: 63.23 mg lactose monohydrate.

PHARMACODYNAMICS AND PHARMACOKINETICS:

Pharmacodynamics

Viacoram Initio/Viacoram combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and perindopril to the angiotensin converting enzyme inhibitors class of medicines. The combination of these substances has an additive antihypertensive effect.

Perindopril: Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough). Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity *in vitro*.

Amlodipine: Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischemic burden by the following two actions:

- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Pharmacokinetics

The rate and extent of absorption of perindopril and amlodipine from Viacoram Initio/Viacoram are not significantly different, respectively, from the rate and extent of absorption of perindopril and amlodipine from individual tablet formulations.

Perindopril:

Absorption: After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Distribution: The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Elimination: Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Amlodipine:

Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg.

VIACORAM®

7 mg/5 mg Tablet
Antihypertensive

In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake. Biotransformation, elimination: The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Special populations:

Pediatric population (age below 18 years): No pharmacokinetic data are available in the pediatric population.

Older people: The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Initiation and increase of the dosage should take place with care in older people depending on renal function.

Elimination of perindoprilat is decreased in the elderly. Renal function should be monitored before increase of the dosage. Therefore, the usual medical follow-up will include monitoring of creatinine and potassium.

Renal impairment: In patients with moderate renal impairment (Creatinine clearance between 30 ml/min to 60 ml/min), the initial recommended dose of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) is 3.5 mg/2.5 mg every other day. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Amlodipine is not dialyzable. Elimination of perindoprilat is decreased in patients with heart or renal failure.

Therefore, the usual medical follow-up will include monitoring of creatinine and potassium.

Hepatic impairment: Caution should be exercised in patients with liver disease.

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Dialysis clearance of perindoprilat is equal to 70 ml/min. Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required.

INDICATION:

Treatment of essential hypertension in adults.

DOSAGE AND ADMINISTRATION:

Posology

Oral use.

Perindopril arginine + Amlodipine besilate (Viacoram Initio) 3.5 mg/2.5 mg is intended for first line therapy in patients with arterial hypertension.

The recommended starting dose is 1 tablet once daily.

After at least four weeks of treatment, the dose may be increased to Perindopril arginine + Amlodipine besilate (Viacoram) 7 mg/5 mg once daily in patients whose blood pressure is not adequately controlled with 3.5 mg/2.5 mg dose.

Special populations

Patients with renal impairment: Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) is contraindicated in patients with severe renal impairment (Creatinine clearance below 30 ml/min).

In patients with moderate renal impairment (Creatinine clearance between 30 ml/min to 60 ml/min), the initial recommended dose is 3.5 mg/2.5 mg every other day.

In patients whose blood pressure is not adequately controlled, the 3.5 mg/2.5 mg dose may be taken once daily. If necessary, the dose may be increased in patients insufficiently controlled. The usual medical follow-up includes monitoring of creatinine and potassium.

Patients with hepatic impairment: Caution should be exercised when prescribing Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) to patients with severe hepatic impairment.

Older people: The efficacy and safety of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) have been established in older people. Caution should be exercised at initiation depending on renal function.

After initiation of the treatment, renal function should be monitored before increase of the dosage, particularly in patients aged 75 years and above.

The usual medical follow-up should include monitoring of creatinine and potassium.

Pediatric population: The safety and efficacy of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) in children aged below 18 years have not been established. No data are available.

Method of administration

The tablet of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) should be taken as a single dose, preferably in the morning and before a meal.

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GENERAL INFORMATIONS

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(710)_VIACORAM INITIO_LGS_001
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PHILIPPINES (PHL)

Font size: 7 / 7 pts
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6 pages

CONTRAINDICATIONS:

- Hypersensitivity to the active substances, to ACE inhibitors, to dihydropyridines derivatives, or to any of the excipients,
- Severe renal impairment,
- History of angioedema associated with previous ACE inhibitor therapy,
- Hereditary or idiopathic angioedema,
- Second and third trimesters of pregnancy,
- Severe hypotension,
- Shock, including cardiogenic shock,
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis),
- Hemodynamically unstable heart failure after acute myocardial infarction,
- Concomitant use of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²).
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces,
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney,
- Concomitant use with sacubitril/valsartan therapy. Perindopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan.

WARNINGS AND PRECAUTIONS:

Special warnings

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril. This may occur at any time during therapy. In such cases, Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan.

Concomitant use of ACE inhibitors with NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE inhibitor.

Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactoid reactions during desensitization:

Patients receiving ACE inhibitors during desensitization treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anemia:

Neutropenia/agranulocytosis, thrombocytopenia and anemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers 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 angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Primary aldosteronism:

Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

Pregnancy:

Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) should not be initiated during pregnancy. Unless continued treatment 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 Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) should be stopped immediately, and, if appropriate, alternative therapy should be started.

Use in patients with renal impairment:

Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) is contraindicated in patients with severe renal impairment (Creatinine clearance below 30 ml/min).

In patients with moderate renal impairment (Creatinine clearance between 30 ml/min to 60 ml/min), the initial recommended dose of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) is 3.5 mg/2.5 mg every other day. The usual medical follow-up in such patients should include monitoring of potassium levels and creatinine.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment.

Amlodipine may be used in patients with renal failure at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Kidney transplantation:

Since there is no experience regarding the administration of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) in patients with a recent kidney transplantation, treatment with Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) is therefore not recommended.

Renovascular hypertension:

There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Use in patients with impaired hepatic function:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) who develop jaundice or marked elevations of hepatic enzymes should discontinue Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) and receive appropriate medical follow-up. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function.

Use in older people:

Initiation and increase of the dosage should take place with care in older people, depending on renal function.

Renal function should be monitored before increase of the dosage. Therefore, the medical follow-up should include monitoring of potassium and creatinine.

Precautions for use

Hypertensive crisis:

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Use in patients with cardiac failure:

Patients with heart failure should be treated with caution. Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) should be used with caution in patients with congestive heart failure, as amlodipine may increase the risk of future cardiovascular events and mortality.

Hypotension:

ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, or who have severe renin-dependent hypertension. In patients at high risk of symptomatic hypotension, blood pressure, renal function and serum potassium should be monitored closely during treatment with Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram).

Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy: ACE inhibitors should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Race: ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

ACE inhibitors may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough: Cough has been reported with the use of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram). Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalemia: Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride, alone or in combination), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, other ACE inhibitors, angiotensin-II antagonists, acetylsalicylic acid \geq 3 g/day, COX-2 inhibitors and non-selective NSAIDs, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and co-trimoxazole also known as trimethoprim/sulfamethoxazole). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) and any of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Diabetic patients: In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram).

Potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes: The combination of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) and potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes is not recommended.

Excipients: This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PREGNANCY AND LACTATION:

Given the effects of the individual components in this combination product on pregnancy and lactation:

Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) is not recommended during the first trimester of pregnancy. It is contraindicated during the second and third trimesters of pregnancy.

Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) taking account the importance of this therapy for the mother.

Pregnancy:

Linked to perindopril:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contraindicated 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. Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy 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 ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension.

Linked to 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 fetus.

Breastfeeding:

Linked to perindopril:

Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Linked to amlodipine:

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. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breastfeeding to the child and the benefit of amlodipine therapy to the mother.

Fertility:

Linked to perindopril:

There was no effect on reproductive performance or fertility.

Linked to 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.

DRIVING AND USING MACHINES:

No studies on the effects of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) on the ability to drive and use machines have been performed.

Perindopril and amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired.

Caution is recommended with Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) especially at the start of treatment.

INTERACTIONS:

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Medicines increasing the risk of angioedema:

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema.

Concomitant use of ACE inhibitors with rabeprazole, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk for angioedema.

Drugs inducing hyperkalemia:

Some drugs or therapeutic classes may increase the occurrence of hyperkalemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and Co-trimoxazole (trimethoprim/sulfamethoxazole). The combination of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) with these drugs increases the risk of hyperkalemia. Therefore, the combination of Viacoram Initio/Viacoram with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Concomitant use contraindicated:

Aliskiren: In diabetic or impaired renal patients, risk of hyperkalemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Extracorporeal treatments: Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or hemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions. If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Sacubitril/valsartan: The concomitant use of perindopril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan.

Concomitant use not recommended:

Estramustine: Risk of increased adverse effects such as angioneurotic edema (angioedema).

Potassium-sparing diuretics (e.g. triamterene, amiloride), potassium (salts): Hyperkalemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalemic effects). ACE inhibitors must not be associated with hyperkalemic substances, except in hypokalemia.

The combination of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) with the above-mentioned drugs is not recommended. If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see below.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Use of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) containing amlodipine, a calcium channel blocker, be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Concomitant use which requires special care:

Antidiabetic agents (insulins, oral hypoglycemic agents): Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Baclofen: Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

Non-potassium-sparing diuretics: Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram).

In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, the diuretic must be discontinued before initiating Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram), in which case a non-potassium-sparing diuretic can be thereafter reintroduced.

Renal function (creatinine levels) must be monitored during the first few weeks of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) therapy.

Potassium-sparing diuretics (epplerenone, spironolactone): With eplerenone or spironolactone at doses between 12.5 mg to 50 mg by day and with low doses of ACE inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction <40%, and previously treated with ACE inhibitors and loop diuretics, risk of hyperkalemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.

Before initiating the combination, check the absence of hyperkalemia and renal impairment.

A close monitoring of the kalemia and creatininemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including aspirin ≥ 3 g/day: When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Cyclosporin: Hyperkalemia may occur during concomitant use of ACE inhibitors with cyclosporin. Monitoring of serum potassium is recommended.

Heparin: Hyperkalemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Racecadotril: ACE inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a drug used against acute diarrhea).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus): Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema.

Gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin): Increased risk of angio-edema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptin, in patients co-treated with an ACE inhibitor.

CYP3A4 inducers: 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*).

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 PK variations may be more pronounced in the elderly. Clinical monitoring and Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) dose adjustment may thus be required.

There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.

Concomitant use which requires some care:

Antihypertensive agents (such as beta-blockers) and vasodilators: Concomitant use of these agents may increase the hypotensive effects of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram). Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.

Tricyclic antidepressants/Antipsychotics/Anesthetics: Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) may result in further reduction of blood pressure.

Sympathomimetics: Sympathomimetics may reduce the antihypertensive effects of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram).

Corticosteroids, tetracosactide: Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin): Increased antihypertensive effect and increased risk of orthostatic hypotension.

Amifostine: May potentiate the antihypertensive effect of amlodipine.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

Grapefruit: Administration of Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) with grapefruit or grapefruit juice is not recommended as amlodipine bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors : mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine: No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

ADVERSE DRUG REACTIONS:

Summary of the safety profile:

The safety profile of Viacoram Initio/Viacoram has been evaluated on a 6-month controlled study involving 1,771 patients, 887 of whom received Viacoram Initio/Viacoram, a 6-week controlled study involving 837 patients, 279 of whom received Viacoram Initio/Viacoram, and an 8-week placebo-controlled study involving 1581 patients, 249 of whom received Viacoram Initio/Viacoram.

In these clinical studies, no significant new adverse reactions were observed with the combination compared to the known effects of the individual monocomponents.

The following adverse reactions were found to be the most frequently reported during clinical trials: dizziness, cough and edema.

The adverse drug reactions previously reported during clinical trials and/or post-marketing experience with one of the individual components (perindopril and amlodipine) have been listed in the following table since they may occur with the fixed-dose combination.

Tabulated list of adverse reactions:

The following undesirable effects have been observed during treatment with Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram), perindopril or amlodipine given separately and ranked under the MedDRA classification by body system and under the following frequency:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ to $< 1/1000$); very rare ($< 1/10000$); not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Viacoram Initio/Viacoram (Perindopril/Amlodipine)	Amlodipine	Perindopril
Infections and infestations	Rhinitis	-	Uncommon	Very rare
Blood and the lymphatic System Disorders	Eosinophilia	-	-	Uncommon*
	Leukopenia/neutropenia	-	Very rare	Very rare
	Agranulocytosis or pancytopenia	-	-	Very rare
	Thrombocytopenia	-	Very rare	Very rare
	Hemolytic anemia enzyme specific in patients with a congenital deficiency of G-6PDH	-	-	Very rare

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Viacoram Initio/ Viacoram (Perindopril/ Amlodipine)	Amlodipine	Perindopril
Immune System Disorders	Hypersensitivity	-	Very rare	Uncommon
Metabolism and Nutrition Disorders	Hyperkalemia	Uncommon	-	Uncommon*
	Hyperglycemia	Uncommon	Very rare	-
	Hyponatremia	-	-	Uncommon*
	Hypoglycemia	-	-	Uncommon*
Psychiatric Disorders	Mood altered (including anxiety)	-	Uncommon	Uncommon
	Insomnia	-	Uncommon	-
	Depression	-	Uncommon	-
	Sleep disorder	-	-	Uncommon
	Confusional state	-	Rare	Very rare
Nervous System Disorders	Dizziness (especially at the beginning of the treatment)	Common	Common	Common
	Headache (especially at the beginning of the treatment)	-	Common	Common
	Somnolence (especially at the beginning of the treatment)	-	Common	Uncommon*
	Dysgeusia	-	Uncommon	Common
	Paresthesia	-	Uncommon	Common
	Syncope	-	Uncommon	Uncommon*
	Hypoesthesia	-	Uncommon	-
	Tremor	-	Uncommon	-
	Hypertonia	-	Very rare	-
	Neuropathy peripheral	-	Very rare	-
Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients	-	-	Very rare	
Eye Disorders	Visual impairment	-	Common	Common
	Diplopia	-	Common	-
Ear and labyrinth Disorders	Tinnitus	-	Uncommon	Common
	Vertigo	-	-	Common
Cardiac Disorders	Palpitations	-	Common	Uncommon*
	Tachycardia	-	-	Uncommon*
	Angina pectoris	-	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients	-	Very rare	Very rare
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	-	Uncommon	Very rare
Vascular Disorders	Flushing	-	Common	-
	Hypotension (and effects related to hypotension)	-	Uncommon	Common
	Vasculitis	-	Very Rare	Uncommon*
	Raynaud's phenomenon	-	-	Not known
Respiratory, Thoracic and Mediastinal Disorders	Cough	Common	Uncommon	Common
	Dyspnea	-	Common	Common
	Bronchospasm	-	-	Uncommon
	Eosinophilic pneumonia	-	-	Very rare
Gastro-intestinal Disorders	Abdominal pain	-	Common	Common
	Nausea	-	Common	Common
	Vomiting	-	Uncommon	Common
	Dyspepsia	-	Common	Common
	Diarrhea	-	Common	Common
	Constipation	-	Common	Common
	Change of bowel habit	-	Common	-
	Dry mouth	-	Uncommon	Uncommon
	Gingival hyperplasia	-	Very rare	-
	Pancreatitis	-	Very rare	Very rare
Gastritis	-	Very rare	-	
Hepato-biliary Disorders	Hepatitis, jaundice	-	Very rare	-
	Hepatitis either cytolytic or cholestatic	-	-	Very rare
Skin and Subcutaneous Tissue Disorders	Rash, exanthema	-	Uncommon	Common
	Pruritus	-	Uncommon	Common
	Hyperhidrosis	-	Uncommon	Uncommon
	Alopecia	-	Uncommon	-
	Purpura	-	Uncommon	-
	Skin discolouration	-	Uncommon	-
	Pemphigoid	-	-	Uncommon*
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx	-	Very rare	Uncommon
	Urticaria	-	Uncommon	Uncommon
	Photosensitivity reaction	-	Very rare	Uncommon*
	Erythema multiforme	Uncommon	Very rare	Very rare
	Quincke's edema	-	Very rare	-
	Stevens-Johnson Syndrome	-	Very rare	-
	Exfoliative dermatitis	-	Very rare	-
	Toxic Epidermal Necrolysis	-	Not known	-
Psoriasis aggravation	-	-	Rare	

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Viacoram Initio/ Viacoram (Perindopril/ Amlodipine)	Amlodipine	Perindopril
Musculoskeletal And Connective Tissue Disorders	Back pain	-	Uncommon	-
	Joint swelling (ankle swelling)	-	Common	-
	Muscle spasms	-	Common	Common
	Arthralgia, myalgia	-	Uncommon	Uncommon*
Renal and Urinary Disorders	Micturition disorder, nocturia, pollakiuria	-	Uncommon	-
	Renal failure	-	-	Uncommon
	Renal failure acute	-	-	Very rare
Reproductive System and Breast Disorders	Erectile dysfunction	-	Uncommon	Uncommon
	Gynecomastia	-	Uncommon	-
General Disorders and Administration Site Conditions	Edema peripheral	Common	-	Uncommon*
	Edema	-	Very common	-
	Fatigue	Uncommon	Common	-
	Asthenia	-	Common	Common
	Chest pain	-	Uncommon	Uncommon*
	Malaise	-	Uncommon	Uncommon*
	Pain	-	Uncommon	-
Pyrexia	-	-	Uncommon*	
Investigations	Weight increased, weight decreased	-	Uncommon	-
	Blood urea increased	-	-	Uncommon*
	Blood creatinine increased	-	-	Uncommon*
	Blood bilirubin increased	-	-	Rare
	Hepatic enzyme increased	-	Very rare	Rare
	Hemoglobin decreased and hematocrit decreased	-	-	Very rare
Injury, poisoning and procedural complications	Fall	-	-	Uncommon*

* Frequency calculated from clinical trials for adverse events detected from spontaneous report

Cases of SIADH have been reported with other ACE inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE inhibitor therapy including perindopril.

Additional information on the combination perindopril/amlodipine:

A randomized, double-blind, placebo-controlled study over 8 weeks demonstrated that peripheral edema, a recognized side effect of amlodipine, was observed at a lower incidence in patients who received the perindopril 3.5 mg/amlodipine 2.5 mg combination than in those who received amlodipine 5 mg alone (1.6% and 4.9% respectively).

REPORTING OF ADVERSE DRUG REACTION:

For suspected adverse drug reaction, report to the FDA at www.fda.gov/ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

OVERDOSE AND TREATMENT:

There is no experience of overdose with Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram).

For amlodipine, experience with intentional overdose in humans is limited.

Symptoms: available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment: clinically significant hypotension due to amlodipine overdosage 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.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

For perindopril, limited data are available for overdosage in humans. Symptoms associated with the overdosage of ACE

inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril can be removed from the systemic circulation by hemodialysis. Pacemaker therapy is indicated for treatment-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

MISSED DOSE:

It is important to take the medicine every day as regular treatment works better. However, if a dose is forgotten, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

DISCONTINUATION OF TREATMENT:

As the treatment with Perindopril arginine + Amlodipine besilate (Viacoram Initio/Viacoram) is usually life-long, discuss with the doctor before stopping the treatment.

For any further questions on the use of this medicine, ask the doctor or pharmacist.

STORAGE CONDITION:

Store at temperatures not exceeding 30°C.

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask the pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

CAUTION:

Food, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

PACKAGING:

Viacoram Initio/Viacoram: Polypropylene tablet container equipped with a low density polyethylene stopper containing a desiccant gel (silica) and a low density polyethylene flow reducer (Box of 30s).



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