PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr VIACORAM®

Perindopril arginine and Amlodipine (as amlodipine besylate) tablets

Tablets, 3.5 mg /2.5 mg Oral
Tablets, 7 mg /5 mg Oral
Tablets, 14 mg /10 mg Oral

Angiotensin converting enzyme inhibitor / Dihydropyridine calcium antagonist

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	[10/2022]
7 WARNING AND PRECAUTIONS	[10/2022]

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VIACORAM® (perindopril arginine and amlodipine) is indicated for:

- The treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.
- VIACORAM® 3.5 mg/2.5 mg is indicated for initial therapy in patients with mild to moderate essential hypertension.
- VIACORAM® is not indicated for switching therapy from the individual drugs currently on the market (perindopril as erbumine or arginine salt, amlodipine) (see 4 DOSAGE AND ADMINISTRATION section).

1.1 Pediatrics (<18 years of age)

VIACORAM® is not indicated in pediatric patients <18 years of age. The efficacy and safety have not been studied in this population.

1.2 Geriatrics (> 65 years of age)

VIACORAM® is not indicated for the initiation of treatment in elderly patients. There is no sufficient clinical experience to justify the use in the elderly (> 65 years).

2 CONTRAINDICATIONS

VIACORAM® (perindopril arginine and amlodipine) is contraindicated in:

- Patients who are hypersensitive to the active ingredients of this drug, to any ingredient in the formulation or component of the container, to any other angiotensin converting enzyme inhibitor (ACE-inhibitor), or to any other dihydropyridine derivatives. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING
- Patients with renal impairment (creatinine clearance < 60 ml/min) (see 7 WARNINGS AND PRECAUTIONS, Renal).
- Patients with a history of hereditary/idiopathic angioedema, or angioedema related to previous treatment with an ACE-inhibitor (see 7 WARNINGS AND PRECAUTIONS, Immune).
- Women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraception. (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant women)
- Nursing women (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Breast-feeding).
- Patients with mitral valve stenosis and left ventricular outflow tract obstruction (e.g. aortic stenosis, hypertrophic cardiomyopathy).
- Patients with heart failure.
- Combination with sacubitril/valsartan due to an increased risk of angioedema. VIACORAM® must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan.
- Combination with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or 2) or moderate to severe renal impairment (GFR < 60ml/min/1.73m^2) (see 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal and 9 DRUG

INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs).

- Patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency as VIACORAM® contains lactose (see 7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).
- Patients with extracorporeal treatments leading to contact of blood with negatively charged surfaces (see 9 DRUG INTERACTIONS).
- Patients with bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney (see 7 WARNINGS AND PRECAUTIONS, Renal).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus.**
- **When pregnancy is detected, VIACORAM® should be discontinued as soon as possible.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

VIACORAM® is a combination product containing perindopril as an arginine salt (perindopril arginine) and amlodipine expressed as free base (amlodipine besylate) and is available in three fixed-dose perindopril arginine/amlodipine combinations of 3.5 mg/2.5 mg, 7 mg/5 mg, and 14 mg/10 mg.

Dosages of the perindopril arginine in VIACORAM® are not marketed individually.

Patients cannot be titrated with the individual drugs currently on the market prior to the initiation of VIACORAM®, since dosages of perindopril arginine in VIACORAM® are not equivalent to those marketed individually (perindopril as erbumine or arginine salt).

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of VIACORAM® is 3.5 mg/2.5 mg once daily in hypertensive patients for whom combination therapy is appropriate.

After 4 weeks of treatment, the dose may be increased to 7 mg/5 mg once daily in adult patients whose blood pressure is not at appropriate target.

If necessary, titration to 14 mg/10 mg once daily may be considered in adult patients insufficiently controlled after 4 weeks of treatment with 7 mg/5 mg.

Pediatrics (<18 years of age):
Health Canada has not authorized an indication for pediatric use.

Elderly (> 65 years of age):

VIACORAM® is not indicated for the initiation of treatment in elderly patients (> 65 years of age).

Hepatic Impairment:

VIACORAM® is not recommended in patients with hepatic impairment (see 7 WARNINGS AND PRECAUTIONS).

Renal Impairment:

VIACORAM® is contraindicated in patients with renal impairment (creatinine clearance <60 ml/min) (see 2 CONTRAINDICATIONS).

Use with Diuretics: In patients who are currently being treated with a diuretic, symptomatic hypotension can occur following the initial dose of VIACORAM®. Consider reducing the dose of diuretic prior to starting VIACORAM® (see 9 DRUG INTERACTIONS, Drug-Drug Interactions).

4.4 Administration

VIACORAM® should be taken as a single dose, preferably in the morning and before a meal.

4.5 Missed Dose

If a dose is missed, a double dose should not be taken, but just carry on with the next dose at the normal time.

5 OVERDOSAGE

There is no experience of overdose with VIACORAM®.

For perindopril, limited data are available for overdosage in humans. The most likely clinical manifestation would be symptoms attributable to severe hypotension.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril can be removed from the systemic circulation by haemodialysis (see 10 CLINICAL PHARMACOLOGY – Special Populations, Renal insufficiency). Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

For amlodipine, experience with overdosage in humans is limited.
Symptoms: available data suggest that overdosage could result in excessive peripheral vasodilatation with marked and probably prolonged hypotension and possibly reflex tachycardia. Shock and 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. Since amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablets 3.5 mg / 2.5 mg, 7 mg / 5 mg and 14 mg / 10 mg	Cellulose, microcrystalline; lactose monohydrate; magnesium stearate; silica, colloidal anhydrous.

Dosage forms

VIACORAM® 3.5 mg/2.5 mg tablets: white, round tablet, 5 mm diameter.
VIACORAM® 7 mg/5 mg tablets: white, round tablet, 6 mm diameter, engraved with on one face.
VIACORAM® 14 mg/10 mg tablets: white, round tablet, 8 mm diameter, engraved with 14/10 on one face and on the other face.

Composition

One tablet of VIACORAM® 3.5 mg/2.5 mg contains 3.5 mg perindopril arginine and 2.5 mg amlodipine.
One tablet of VIACORAM® 7 mg/5 mg contains 7 mg perindopril arginine and to 5 mg amlodipine.
One tablet of VIACORAM® 14 mg/10 mg contains 14 mg perindopril arginine and 10 mg amlodipine.

The other ingredients are: cellulose microcrystalline, colloidal anhydrous silica, lactose monohydrate, magnesium stearate.

Packaging

- VIACORAM® 3.5 mg/2.5 mg tablets & VIACORAM® 7 mg/5 mg tablets:

30 or 100 tablets in polypropylene container equipped with a low-density polyethylene flow reducer and a low-density polyethylene stopper containing a desiccant gel (silica).

- Box of 1 container of 30 tablets.
- Box of 2 containers of 30 tablets.
- Box of 3 containers of 30 tablets.
- Box of 1 container of 100 tablets.
- Box of 5 containers of 100 tablets.

- VIACORAM® 14 mg/10 mg tablets:

30 tablets in polypropylene container equipped with a low-density polyethylene flow reducer and a low-density polyethylene stopper containing a desiccant gel (silica).

- Box of 1 container of 30 tablets.
- Box of 2 containers of 30 tablets.
- Box of 3 containers of 30 tablets.

Not all pack sizes may be marketed.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Cardiovascular

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

VIACORAM® is contraindicated in patients with mitral valve stenosis and obstruction in the outflow tract of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin converting enzyme (ACE) inhibitors, such as the perindopril component of VIACORAM®, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60ml/min/1.73m^2). Therefore, the use of VIACORAM® in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including the perindopril component of VIACORAM®, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia (see 9 DRUG INTERACTIONS).

Hypotension

VIACORAM® can cause symptomatic hypotension. 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 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.

Peripheral Oedema

Mild to moderate peripheral oedema was the most common adverse event in the clinical trials with amlodipine. The incidence of peripheral oedema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Peripheral oedema is also one of the most frequently occurring adverse drug reactions that resulted in discontinuation of VIACORAM®. Care should be taken to differentiate this peripheral oedema from the effects of increasing left ventricular dysfunction.

Patients with Heart Failure

Patients with heart failure were excluded from the clinical trials for VIACORAM®. VIACORAM® should not be used in patients with congestive heart failure.

Hypertensive Crisis
The safety and efficacy of VIACORAM® in hypertensive crisis has not been established.

Increased Angina and/or Myocardial Infarction
Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of VIACORAM®, particularly in patients with severe obstructive coronary artery disease.

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the RAS. Therefore, the use of VIACORAM® is not recommended in these patients.

Driving and Operating Machinery

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 VIACORAM® especially at the start of treatment.

Endocrine and Metabolism

Hyperkalemia
Monitor serum potassium periodically in patients receiving VIACORAM®.

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, ARBs, cyclooxygenase-2 (COX-2) inhibitors and non-selective non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressant agents such as cyclosporine or tacrolimus, trimethoprim and fixed dose combination with sulfamethoxazole).

VIACORAM® is not recommended for concomitant use with potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes, particularly in patients with impaired renal function (see 9 DRUG INTERACTIONS, Drug-Drug Interactions).

Hyperkalemia (serum potassium >5.5 mEq/L) can cause serious, sometimes fatal arrhythmias. If concomitant use of VIACORAM® and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Hematologic

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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. 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 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) to their physician (see 7 WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests section).

Hepatic/Biliary/Pancreatic

Patients with Impaired Liver Function

Increases in serum transaminase and/or bilirubin levels, cholestatic jaundice and cases of hepatocellular injury with or without cholestasis have occurred during ACE inhibitor therapy, even in patients with no pre-existing liver disease. Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death.

In a small number of patients with mild to moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged.

VIACORAM® is not recommended in patients with impaired liver.

Immune

Angioedema – Head, and Neck or Extremities

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including perindopril. This may be life-threatening and occur at any time during therapy. In such cases, 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 oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction and may be fatal, emergency therapy should be administered promptly. This may include the administration of epinephrine (e.g., 0.3 to 0.5 ml of subcutaneous epinephrine solution 1:1000) 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 VIACORAM® (see 2 CONTRAINDICATIONS).

Concomitant use of mTOR inhibitors, DPP-IV inhibitors and NEP inhibitors

Patients taking a concomitant mTOR inhibitor (e.g. sirolimus, everolimus, temsirolimus), DPP-IV inhibitor (e.g. sitagliptin, linagliptin, saxagliptin) or neutral endopeptidase (NEP) inhibitor may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment). Caution should be used when initiating ACE inhibitor therapy in patients already taking a mTOR, DPP-IV or NEP inhibitor or vice versa (see 9 DRUG INTERACTIONS).

Intestinal Angioedema

Intestinal angioedema has been reported 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 history of facial angioedema and C-1 esterase levels were normal.

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.

Anaphylactoid Reactions during Low-Density Lipoproteins (LDL) Apheresis

Rarely, patients receiving ACE inhibitors during 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.

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Anaphylactoid Reactions during Desensitisation

Patients receiving ACE inhibitors during desensitisation 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.

Anaphylactoid Reactions during Membrane Exposure (hemodialysis patients)

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Nitritoid Reactions – Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting, and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including VIACORAM® (see 9 DRUG INTERACTIONS).

Monitoring and Laboratory Tests

Hematological monitoring

It is recommended that the white blood cell count be monitored to permit detection of a possible leukopenia.

Renal function monitoring

Use of VIACORAM® should include appropriate assessment of renal function, particularly in the first few

weeks of treatment after initiation of therapy, or up titration. Potassium and creatinine should be monitored periodically thereafter.

Serum Electrolyte monitoring
It is recommended that serum potassium and serum sodium be monitored regularly. More frequent monitoring of serum potassium is necessary in patients with impaired renal function.

Peri-Operative Considerations

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. 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.

Race

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.
ACE inhibitors are generally 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.

Renal

Impaired Renal Function
VIACORAM® is contraindicated in patients with renal impairment (creatinine clearance < 60 ml/min) (see 2 CONTRAINDICATIONS).

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals treated with VIACORAM®. Potassium and creatinine should be monitored in patients treated with VIACORAM®.

The use of ACE inhibitors, including perindopril which is a component of VIACORAM®, or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2) (See 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors, or aliskiren-containing drugs).

Hypertensive Patients with Renal Artery Stenosis
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 nitrogen (BUN) 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 BUN 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.

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors (see 2 CONTRAINDICATIONS). 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.

Kidney transplantation
Since there is no experience regarding the administration of VIACORAM® in patients with a recent kidney transplantation, treatment with VIACORAM® is therefore not recommended.

Reproductive Health: Female and Male Potential

Sextual Function/Reproduction
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 (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and developmental toxicity

Respiratory

Cough
Cough has been reported with the use of VIACORAM®. Characteristically, the cough is dry, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Sensitivity/Resistance

Due to the presence of lactose, patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption or the Lapp lactase deficiency should not take VIACORAM® (see 2 CONTRAINDICATIONS).

Skin

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity has been reported with another ACE inhibitor. Rare and sometimes severe skin reactions (lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome, etc) have occurred.

Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross-reactivity.

Stevens-Johnson syndrome occurred in ≤ 0.1% of patients in clinical trials with amlodipine.

7.1 Special Populations

7.1.1 Pregnant Women

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant

women. VIACORAM® is contraindicated during pregnancy.

Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is detected, treatment with VIACORAM® should be stopped immediately, and an alternative therapy should be started.

7.1.2 Breast-feeding

The presence of ACE inhibitor in human milk has been reported. Amlodipine is excreted in human milk. The minimum proportion of the maternal dose received by the infant has been estimated to be between 3 and 15% and this might vary according to breastmilk composition. The effect of amlodipine on infants is unknown. The use of VIACORAM® is contraindicated during breastfeeding (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics (<18 years of age)

The safety and effectiveness of VIACORAM® in patients below the age of 18 have not been established. Therefore, use in this age group is not recommended.

7.1.4 Geriatrics (>65 years of age)

VIACORAM® is not indicated for the initiation of treatment in the elderly (> 65 years) patients. Greater sensitivity of some older individuals cannot be ruled out.

7.1.5 Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with VIACORAM® (see 9 DRUG INTERACTIONS, Drug-Drug Interactions).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions were the most frequently reported during clinical trials: cough, dizziness, headache, and oedema.

The most serious adverse reactions reported during clinical trials were: hypotension, lip swelling, and renal failure acute.

The adverse drug reactions most frequently resulting in clinical intervention (discontinuation of VIACORAM®) were due to cough, erythema, fatigue, and peripheral oedema.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

CL2-005 study

The most frequent adverse events during the 8-week placebo-controlled study CL2-005 are presented in Table 2

Table 2 - Most Frequently Reported Emergent Adverse Events (≥ 1%)

Emergent Adverse events	Per 3.5/Aml 2.5 (N = 249) %	Placebo (N = 251) %	Per 3.5 mg (N = 273) %	Aml 2.5 mg (N = 274) %	Per 5 mg (N = 272) %	Aml 5 mg (N = 264) %
Metabolism and nutrition disorders						
Hyperkalaemia	6 (2.4)	0	0	6 (2.2)	2 (0.7)	1 (0.4)
General disorders						
Oedema peripheral	4 (1.6)	3 (1.2)	8 (2.9)	2 (0.7)	4 (1.5)	13 (4.9)
Nervous system disorders						
Headache	3 (1.2)	4 (1.6)	5 (1.8)	4 (1.5)	3 (1.1)	1 (0.4)
Respiratory, thoracic and mediastinal disorders						
Cough	2 (0.8)	1 (0.4)	3 (1.1)	2 (0.7)	3 (1.1)	1 (0.4)
Nasopharyngitis	3 (1.2)	1 (0.4)	2 (0.7)	3 (1.1)	2 (0.7)	3 (1.1)
Vascular disorders						
Hot flush / Flushing	1 (0.4)	0	2 (0.7)	0	0	5 (1.9)
Investigations						
Creatinine renal clearance decreased	3 (1.2)	1 (0.4)	0	2 (0.7)	2 (0.7)	1 (0.4)
Blood glucose increased	1 (0.4)	0	1 (0.4)	0	3 (1.1)	0
Musculoskeletal and connective tissue disorders						
Back pain	1 (0.4)	1 (0.4)	0	2 (0.7)	2 (0.7)	5 (1.9)

Aml : Amlodipine; Per: Perindopril

PATH study

The most frequent emergent adverse events (EAEs) during the 6-week active controlled PATH study are presented in Table 3.

Table 3 - Most Frequently Reported Emergent Adverse events (≥ 1%)

System Organ Class Preferred Term	PERa 14/Aml 10 N = 279 (%)	PERe 16 N = 278 (%)	Aml 10 N = 280 (%)
Patients with any EAE	86 (30.8)	77 (27.7)	108 (38.6)
General disorders	28 (10.0)	6 (2.2)	44 (15.7)
Oedema peripheral	20 (7.2)	1 (0.4)	35 (12.5)
Fatigue	5 (1.8)	4 (1.4)	2 (0.7)
Nervous system disorders	18 (6.5)	17 (6.1)	14 (5.0)

System Organ Class Preferred Term	**PERa 14/Aml 10** N = 279 **(%)**	**PERe 16** N = 278 **(%)**	**Aml 10** N = 280 **(%)**
Headache	7 (2.5)	8 (2.9)	8 (2.9)
Dizziness	7 (2.5)	4 (1.4)	3 (1.1)
Gastrointestinal disorders	11 (3.9)	19 (6.8)	10 (3.6)
Diarrhea	3 (1.1)	5 (1.8)	1 (0.4)
Nausea	2 (0.7)	4 (1.4)	2 (0.7)
Infections and Infestations	15 (5.4)	10 (3.6)	10 (3.6)
Nasopharyngitis	3 (1.1)	0 (0.0)	1 (0.4)
Urinary tract infection	4 (1.4)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorder	11 (3.9)	11 (4.0)	9 (3.2)
Arthralgia	2 (0.7)	3 (1.1)	2 (0.7)
Back pain	3 (1.1)	1 (0.4)	2 (0.7)
Musculoskeletal pain	2 (0.7)	3 (1.1)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	14 (5.0)	10 (3.6)	5 (1.8)
Cough	9 (3.2)	8 (2.9)	2 (0.7)
Investigations	4 (1.4)	11 (4.0)	11 (3.9)
Alanine aminotransferase increased	0 (0.0)	4 (1.4)	0 (0.0)
Aspartate aminotransferase increased	1 (0.4)	3 (1.1)	0 (0.0)
Blood potassium increased	0 (0.0)	3 (1.1)	0 (0.0)
Skin and subcutaneous tissue disorders	10 (3.6)	4 (1.4)	12 (4.3)
Erythema	3 (1.1)	1 (0.4)	0 (0.0)
Rash	1 (0.4)	0 (0.0)	3 (1.1)
Renal and urinary disorders	4 (1.4)	4 (1.4)	9 (3.2)
Hematuria	2 (0.7)	1 (0.4)	3 (1.1)
Pollakiuria	1 (0.4)	0 (0.0)	4 (1.4)

Aml: Amlodipine; EAE: Emergent Adverse Event; PERa: Perindopril arginine; PERe: Perindopril erbumine

8.3 Less Common Clinical Trial Adverse Reactions (<1%)

The following adverse drug reactions occurred in patients treated with VIACORAM® in randomized, double-blind controlled trials (<1% but >0.1%):

Blood and lymphatic system disorders: leukopenia, thrombocytopenia
Cardiac disorders: angina pectoris, atrial fibrillation, chest pain, myocardial infarction, sinus tachycardia
Gastrointestinal disorders: constipation, diarrhea, dry mouth, vomiting
General disorders and administration site conditions: asthenia
Immune system disorders: angioedema, dermatitis allergic, pruritus allergic
Investigations: creatinine renal clearance decreased, gamma-glutamyltransferase increased
Musculoskeletal and connective tissue disorders: arthralgia, muscle spasms, myalgia
Nervous system disorders: cerebrovascular accident, ischemic stroke, syncope, transient ischemic attack
Psychiatric disorders: insomnia, depression
Reproductive system and breast disorders: erectile dysfunction
Skin and subcutaneous tissue disorders: hyperhidrosis
Vascular disorders: hot flush, hypotension, orthostatic hypotension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

The following were observed in patients treated with perindopril:
- Abnormal liver function test
- Hyperkalemia
- Increases in blood creatinine, BUN, serum cholesterol and plasma glucose.
- Decreases in hematocrit and hemoglobin.

8.5 Post-Market Adverse Reactions

The most commonly reported adverse reactions with perindopril and amlodipine given separately are: abdominal pain, change of bowel habits, dysgeusia, dyspepsia, dyspnea, exanthema, joint swelling (ankle swelling), palpitations, paraesthesia, prurit, somnolence, tinnitus, vertigo, visual impairment (including diplopia).

The other adverse drug reactions previously reported during clinical trials and/or post-marketing experience with one of the individual components of VIACORAM® are listed below since they may occur with the fixed-dose combination:

Blood and lymphatic system disorders: agranulocytosis or pancytopenia, eosinophilia, leukopenia/neutropenia, haemolytic anaemia enzyme specific in patients with a congenital deficiency of G-6PDH
Cardiac disorders: arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), tachycardia
Endocrine disorders: syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Gastrointestinal disorders: gastritis, gingival hyperplasia, pancreatitis
General disorders and administration site conditions: chest pain, malaise, pain, pyrexia
Hepato-biliary disorders: hepatitis, hepatitis either cytolytic or cholestatic, jaundice
Immune system disorders: hypersensitivity
Infections and infestations: rhinitis

Injury, poisoning and procedural complications: fall
Investigations: blood bilirubin increased, blood urea increased, hepatic enzyme increased, weight decreased, weight increased
Metabolism and nutrition disorders: hyperglycaemia, hypoglycaemia, hyponatraemia
Nervous system disorders: cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients, extrapyramidal disorder (extrapyramidal syndrome), hypoaesthesia, hypertonia, neuropathy peripheral, tremor
Psychiatric disorders: confusional state, mood altered (including anxiety), sleep disorder, depression
Renal and urinary disorders: micturition disorder, nocturia, renal failure, anuria/oliguria
Reproductive system and breast disorders: gynaecomastia
Respiratory, thoracic and mediastinal disorders: bronchospasm, eosinophilic pneumonia
Skin and subcutaneous tissue disorders: alopecia, angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, erythema multiforme, exfoliative dermatitis, pemphigoid, photosensitivity reaction, psoriasis aggravation, purpura, Quincke's oedema, skin discolouration, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticarial
Vascular disorders: Raynaud's phenomenon, vasculitis, flushing

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Lifestyle interactions have not been established.

9.4 Drug-Drug Interactions

Table 4 - Established or Potential Concomitant Drug-Drug Interactions

Proper name	Source of Evidence	Effect	Clinical comment
Agents Increasing Serum Potassium	CT	Since VIACORAM® decreases aldosterone production, elevation of serum potassium may occur.	VIACORAM® is not recommended for concomitant use with potassium-sparing diuretics (such as spironolactone, eplerenone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes, or any drugs associated with increase in serum potassium (heparin, NSAIDs, immunosuppressant agents such as cyclosporin and tacrolimus, angiotensin receptor blockers and others), since they may lead to a significant increase in serum potassium. If concomitant use of VIACORAM® and any of the above-mentioned agents is deemed appropriate, they should be used with caution and frequent monitoring of serum potassium.

Table 4 - Established or Potential Concomitant Drug-Drug Interactions			
Proper name	**Source of Evidence**	**Effect**	**Clinical comment**
Antidiabetic agents (insulins, oral hypoglycaemic agents)		Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines may cause an increased blood-glucose lowering effect with risk of hypoglycaemia.	This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.
Antihypertensive agents and vasodilators		Concomitant use of these agents may increase the hypotensive effects of VIACORAM®. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.	Concomitant use with these agents should be considered with caution.
Baclofen		Increased antihypertensive effect.	Monitor blood pressure and adapt antihypertensive dosage if necessary.
Clarithromycin	CT	In elderly patients (>65 years of age), concomitant use of amlodipine with clarithromycin was associated with increased risk of hospitalization with acute kidney injury. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine.	Avoid concomitant use. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.
Corticosteroids	T	Corticosteroids cause salt and water retention. Therefore, concomitant use with corticosteroids may reduce the antihypertensive effects of VIACORAM®.	Monitor blood pressure.

Table 4 - Established or Potential Concomitant Drug-Drug Interactions

Proper name	Source of Evidence	Effect	Clinical comment
Cyclosporin	CT	No drug interaction studies have been conducted with cyclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients (N=11), where an average of 40% increase in trough concentrations of cyclosporin was observed.	Consideration should be given for monitoring cyclosporin levels in renal transplant patients on VIACORAM®, and cyclosporin dose reductions should be made as necessary.
CYP3A4 inducers (e.g., rifampicin, carbamazepine)	T	The concomitant use of amlodipine and CYP3A4 inducers may reduce the plasma concentration of amlodipine.	Monitor blood pressure. Consider dose regulation both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin). VIACORAM® should be used with caution together with CYP3A4 inducers.
CYP3A4 inhibitors (protease inhibitors like indinavir and ritonavir; azole antifungals like ketoconazole and itraconazole; macrolides like erythromycin and clarithromycin; verapamil, diltiazem)	T	Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors may significantly increase amlodipine exposure.	Clinical monitoring (e.g., symptoms of hypotension and oedema) are required. VIACORAM® dose adjustment may be needed.
Diuretics	C	Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted may experience an excessive reduction of blood pressure after initiation of therapy.	The possibility of hypotensive effects with VIACORAM® can be minimized by increasing the salt intake prior to initiation of treatment with VIACORAM®. If diuretic therapy cannot be altered, provide close medical supervision with the first dose of VIACORAM®, for ≥2 hours and until blood pressure has stabilized for another hour.

Table 4 - Established or Potential Concomitant Drug-Drug Interactions

Proper name	Source of Evidence	Effect	Clinical comment
DDP-IV inhibitors (linagliptin, saxagliptin, sitagliptin)		Increased risk of angioedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptins, in patients co-treated with an ACE inhibitor.	Caution should be used when initiating VIACORAM® in patients already taking a DPP-IV inhibitor or *vice versa* (see 7 WARNINGS AND PRECAUTIONS, Immune, Head and Neck Angioedema).
Dual blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs	CT	Dual blockade of the RAS with ACE inhibitors, ARBs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).
Estramustine		Risk of increased adverse effects such as angioneurotic oedema (angioedema).	Use with caution when VIACORAM® is co-administered with estramustine.
Extracorporeal treatments		Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration 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 (see 2 CONTRAINDICATIONS).	If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.
Gold salts	CT	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.	Use with caution when VIACORAM® is co-administered with gold salts.

Table 4 - Established or Potential Concomitant Drug-Drug Interactions			
Proper name	**Source of Evidence**	**Effect**	**Clinical comment**
Lithium	C	Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy.	These drugs should be co-administered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be further increased.
mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)	CT T	Patients taking concomitant mTOR inhibitors may be at increased risk for angioedema. 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.	Caution should be used when initiating VIACORAM® in patients already taking mTOR inhibitors or *vice versa* (see 7 WARNINGS AND PRECAUTIONS, Head and Neck Angioedema).
Non-steroidal anti-inflammatory drugs (NSAIDs)	CT	The antihypertensive effects of ACE-inhibitors, including the perindopril component of VIACORAM® may be attenuated by NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), when they are co-administrated. Concomitant use of VIACORAM® and NSAIDs may result in deterioration of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with pre-existing renal impairment, dehydration or who are elderly.	The combination of VIACORAM® and NSAIDs should be administered with caution. Patients should be adequately hydrated. Monitor renal function after initiation of concomitant therapy, and periodically thereafter.

Table 4 - Established or Potential Concomitant Drug-Drug Interactions

Proper name	Source of Evidence	Effect	Clinical comment
Neutral endopeptidase inhibitor		ACE inhibitors are known to cause angioedema. This risk may be elevated when used concomitantly with a neutral endopeptidase inhibitor	Caution should be used when initiating VIACORAM® in patients already taking a neutral endopeptidase inhibitor or vice versa (see 7 WARNINGS AND PRECAUTIONS, General, Head and Neck Angioedema).
Sacubitril/Valsartan		The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see 2 CONTRAINDICATIONS).	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 (see 2 CONTRAINDICATIONS).
Simvastatin	CT	Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone.	Limit the dose of simvastatin to 20 mg daily in patients on VIACORAM® 14 mg/10 mg.
Sympathomimetics		Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.	Use with caution when VIACORAM® is co-administered with sympathomimetics.
Tacrolimus	C	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 adjustments of tacrolimus when appropriate.
Tetracosactide	T	Tetracosactide cause salt and water retention. Therefore, concomitant use with tetracosactide may reduce the antihypertensive effects of VIACORAM®.	Monitor blood pressure.
Tricyclic antidepressants /Antipsychotic / Anesthetics		Concomitant use of certain anesthetics, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure.	Use with caution when VIACORAM® is co-administered with these drugs.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical.

9.5 Drug-Food Interactions

Administration of 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.

9.6 Drug-Herb Interactions

The concomitant use of CYP3A4 inducers such as St. John's wort (hypericum perforatum) may give a lower plasma concentration of amlodipine. Consider dose regulation both during and after concomitant medication particularly with strong CYP3A4 inducers. VIACORAM® should be used with caution together with CYP3A4 inducers.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory products/methods have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

VIACORAM® combines two compounds: amlodipine belonging to the dihydropyridine calcium antagonist (calcium channel blocker) class and perindopril belonging to the angiotensin converting enzyme (ACE) inhibitor class of medicines.

Perindopril

Following oral administration, perindopril is rapidly hydrolysed to perindoprilat, its principal active metabolite. ACE catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.
Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and decreased aldosterone secretion. The latter change may result in a small increase in serum potassium (see 7 WARNINGS AND PRECAUTIONS - Endocrine and Metabolism).

Decreased levels of angiotensin II and the accompanying lack of negative feedback on renin secretion leads to increased plasma renin activity.
ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of VIACORAM® remains to be elucidated.

The mechanism through which perindopril lowers blood pressure appears to be primarily suppression of the renin-angiotensin-aldosterone system (RAAS).

Amlodipine

Amlodipine is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist).
Amlodipine is a member of the dihydropyridine class of calcium antagonists. The therapeutic effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine

inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells.
Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound, and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

10.2 Pharmacodynamics

Perindopril
In most patients with mild to moderate essential hypertension, administration of 4 to 8 mg daily of perindopril erbumine (equivalent to 5 to 10 mg/day perindopril arginine) results in a reduction of both supine and standing blood pressure with little or no effect on heart rate. Antihypertensive activity commences within 1 hour with peak effects usually achieved by 4 to 6 hours after dosing. At recommended doses given once daily, antihypertensive effects persist over 24 hours. The blood pressure reductions observed at trough plasma concentration were 75-100% of peak effects.
Amlodipine
Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. With chronic once daily oral administration (5 and 10 mg once daily), antihypertensive effectiveness is maintained throughout the 24 hours dose interval with minimal peak to trough differences in plasma concentration.

Negative inotropic effects have not been observed when amlodipine was administered at the recommended doses to man but has been demonstrated in animal models. Hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in angina patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume.

Amlodipine does not change sinoatrial (SA) nodal function or atrioventricular (AV) conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with β-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

10.3 Pharmacokinetics

The rate and extent of absorption of perindopril and amlodipine from VIACORAM® are not significantly different from the rate and extent of absorption of perindopril and amlodipine from individual tablet formulations.

Table 5: Summary of Perindopril/Perindoprilat and Amlodipine's Pharmacokinetic Parameters (Geometric Mean (CV%)) Following Single Administration of VIACORAM® (14mg/10mg) in Healthy Volunteers (PKH-05985-009)

Single dose mean	C_{max}(ng/mL)	$t_{½}$ (h) *	$AUC_{0-\infty}$(ng*h/mL)
Perindopril	95.4 (41%)	0.68 (0.54 – 0.88)	120 (17%)

Single dose mean	C_{max}(ng/mL)	$t_{½}$ (h) *	$AUC_{0-\infty}$(ng*h/mL)
Perindoprilat	16.1 (46%)	113 (45 – 151)	341 (23%)
Amlodipine	5.97 (25%)	45 (31 – 57)	276 (27%)

** : median and range*

Perindopril

Absorption
After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved at about 1 hour.

About 25% of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. The peak plasma concentration of perindoprilat is in about 4 hours after oral administration of perindopril.

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

Distribution
The volume of distribution is approximately 0.5 L/kg for unbound perindoprilat. Plasma protein binding of perindoprilat is 10 to 35%, principally to angiotensin converting enzyme, but is concentration dependent.

Metabolism:
Perindopril is extensively metabolised following oral administration, with only 4 to 12% of the dose recovered unchanged in the urine. In addition to active perindoprilat, perindopril yields five other metabolites (perindopril glucuronide, perindoprilat glucuronide, a perindopril lactam, and two perindoprilat lactams), all inactive.

The two main circulating metabolites of perindopril are perindoprilat and perindoprilat glucuronide.

Elimination
The terminal plasma half-life of perindopril is 1.2 hour. Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 3-4 days.

Amlodipine

Absorption
After oral administration of therapeutic doses, absorption of amlodipine occurs gradually with peak plasma concentration reached between 6-12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not affected by food intake.

Distribution
The volume of distribution is approximately 21 l/kg. Ex vivo studies have shown that approximately 93% of circulating amlodipine is bound to plasma proteins.

Metabolism
Amlodipine is extensively (about 90%) metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Elimination
The terminal plasma elimination half-life is about 35-50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Special Populations and Conditions

- **Pediatrics (<18 years of age)** No pharmacokinetic data are available in the pediatric population.
- **Geriatrics (>65 years of age)** Elimination of perindoprilat is decreased in the elderly.
  In elderly patients, amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life.
- **Sex** The effectiveness of VIACORAM® was not influenced by gender.
- **Genetic Polymorphism** Pharmacokinetics differences due to genetic polymorphism have not been studied.
- **Ethnic Origin** The blood pressure lowering effects of ACE inhibitors generally are lower in black persons than Caucasian patients. The cardiovascular benefits of ACE inhibitors, in terms of risk reduction in coronary artery disease, have not been extensively studied in blacks.
- **Hepatic Insufficiency** VIACORAM® is not recommended in patients with impaired liver function (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

  The bioavailability of perindoprilat is increased in patients with impaired hepatic function. Plasma concentrations in patients with hepatic impairment were about 50% higher than those observed in healthy subjects or hypertensive patients with normal liver function.

  Following single oral administration of 5 mg of amlodipine, patients with chronic mild to moderate hepatic insufficiency showed about 40% increase in AUC of amlodipine as compared to normal volunteers. The terminal elimination half-life of amlodipine was prolonged from 34 hours in young normal subjects to 56 hours in the elderly patients with hepatic insufficiency.
- **Renal Insufficiency** In patients with renal insufficiency, perindoprilat AUC increases with decreasing renal function. At creatinine clearances of 30-80 ml/min, AUC is about double that of 100 ml/min. When creatinine clearance drops below 30 ml/min, AUC increases more markedly.

  Therefore, VIACORAM® is contraindicated in patients with renal impairment (creatinine clearance < 60 ml/min) (see 2 CONTRAINDICATIONS, 7 WARNINGS and PRECAUTIONS - Renal).

  Perindopril and perindoprilat are dialyzable.

  The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Plasma concentrations of amlodipine in the patients with moderate to severe renal failure were higher than in the normal subjects. Amlodipine is not dialyzable.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C – 30°C. Protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

VIACORAM® is a combination of perindopril arginine and amlodipine besylate.

Drug Substance

Perindopril

Proper name: Perindopril arginine

Chemical name: L-arginine (2S, 3aS, 7aS) -1 - [(2S) - 2-[[(1S) - 1 -ethoxycarbonyl)butyl] amino] propanoyl] octahydro-1H-indole-2-carboxylate

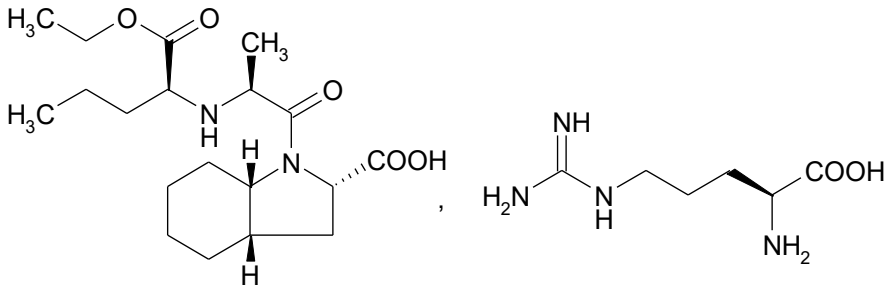
or as a synonym:

(2S, 3aS, 7aS) -1 - [(S) - N - [(S) - 1 - ethoxycarbonyl)butyl] alanyl] octahydro - 1H- indole-2-carboxylic acid, arginine salt

Molecular formula and molecular mass: $C_{19}H_{32}N_2O_5$, $C_6H_{14}N_4O_2$

368.47 (perindopril)/542.7 (perindopril arginine)

Structural formula:



Physicochemical properties: White to almost white powder, freely soluble in water and slightly soluble in ethanol 96 % (V/V) and practically insoluble in methylene chloride.

The pH in aqueous solution (10 mg/mL) is 7.5.

The pKa value for the NH^{2+}/NH pair is 5.66, and 3.50 for the COOH/ COO^- pair.

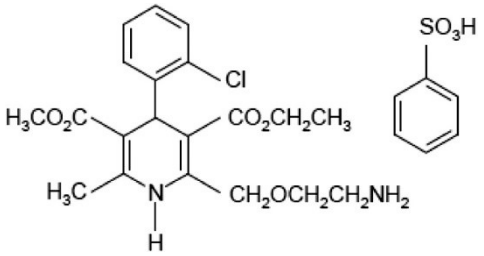
Amlodipine

Proper Name: Amlodipine besylate

Chemical Name: 3-Ethyl-5-methyl(4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydro-pyridine-3,5-dicarboxylate benzenesulphonate.

Molecular Formula and molecular mass: $C_{20}H_{25}ClN_2O_5$, $C_6H_6O_3S$
567.1

Structural Formula:



Physicochemical properties: Amlodipine besylate is a white crystalline substance.
Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol.
M.P.= 203ºC with decomposition.
The pKa = 9.02 at 23.5ºC.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Study CL2-005

In this 8-week randomized, double-blind, placebo-controlled, parallel group factorial study, a total of 1581 patients with mild to moderate uncomplicated essential hypertension (i.e. not at high cardiovascular risk and without target organ damages, 95 mmHg ≤ supine diastolic blood pressure (DBP) < 110 mmHg and 150 mmHg ≤ supine systolic blood pressure (SBP) <180 mmHg, mean baseline SBP/ DBP was 161/101 mmHg) received treatment with perindopril arginine 3.5 mg/amlodipine 2.5 mg, perindopril arginine 3.5 mg, perindopril arginine 5 mg, amlodipine 2.5 mg, amlodipine 5 mg, or placebo. The mean age of the population was 52 years with most patients (86.7%) <65 years, 47% were male, mean BMI was 26.8 kg/m², 98.6% were Caucasian, and 1.1% were Black. The mean time since diagnosis of hypertension was 4 years and 8 months. There were 965 (39%) patients who did not receive treatment for hypertension prior to the selection. No patients included had a history of diabetes.

Table 6 - Summary of Patient Demographics and Trial Design for Study CL2-005

Study	Study design	Dosage, route of administration and duration	# Study subjects (n) randomized	Mean age (Range) Mean ± SD	Sex (%) M/F
CL2-005	Phase 2/3, multicenter, randomized, double-blind, placebo-controlled, parallel group factorial study	Oral administration of PERa 3.5mg/AML 2.5 mg, placebo, PERa 3.5 mg, AML 2.5 mg, PERa 5 mg, AML 5 mg, Treatment duration: 8 weeks	Total 1581 248 250 273 274 272 264	51.7 ± 11.4	46.7 / 53.3

AML: Amlodipine; F: Female; M: Male; PERa: Perindopril arginine; SD: Standard deviation

PATH Study

The highest strength of perindopril arginine/amlodipine (14 mg/10 mg) was studied in a randomised, double-blind, active controlled trial in hypertensive patients (mean seated DBP ≥ 95 and ≤ 115 mmHg, mean seated SBP< 180 mmHg, and the mean baseline SBP/DBP was 158/101 mmHg).

A total of 837 U.S. hypertensive patients received treatments of perindopril arginine 14 mg/amlodipine 10 mg (n=271), perindopril erbumine 16 mg (n=274, corresponding to 20 mg of perindopril arginine), or amlodipine 10 mg (n=275) once daily for 6 weeks. The mean age of the population was 51 years with most of the patients (92.8%) having <65 years, 51% of patients were male, and 34% were Black. Overall, 20% of the population had type 2 diabetes. The population was largely obese with the mean BMI equal to 33.1 kg/m^2. There were 270 (32%) patients who did not receive treatment for hypertension prior to selection. Patients with renal insufficiency were not allowed to take part in this study.

Table 7– Summary of Patient Demographics and Trial Design for PATH Study

Study	Study design	Dosage, route of administration and duration	# Study subjects (n) randomized	Mean age (Range)	Sex (%) M/F
PATH	Phase 3, multicenter, randomized, double-blind, active controlled, parallel group study	Oral administration of PERa 14mg/AML 10mg, PERe 16 mg, AML 10 mg. Treatment duration: 6 weeks	Total 837 279 278 280	51.2 ± 9.7	51.4 / 48.6

AML: Amlodipine; F: Female; M: Male; PERa: Perindopril arginine; ; PERe: Perindopril erbumine ,SD: Standard deviation

Study CL2-005

Perindopril 3.5 mg/amlodipine 2.5 mg was superior to placebo on reducing SBP/DBP (estimate of the difference of the change from baseline to last post-baseline value was -7.2/-4.1 mmHg, p<0.001 for both). The controlled rate (SBP<140 mmHg and DBP<90 mmHg) by perindopril 3.5 mg/amlodipine 2.5

mg was superior to placebo (43.5% *versus* 26.6%, p<0.001).

Perindopril 3.5 mg/amlodipine 2.5 mg was superior to perindopril 3.5 mg and amlodipine 2.5 mg administered separately on reducing SBP/DBP (estimate of the difference of SBP/DBP reduction between treatments was -5.0/-3.6 mmHg and -5.2/-3.0 mmHg as compared to perindopril 3.5 mg and amlodipine 2.5 mg, respectively, p<0.001 for all comparisons).

See results summarized in Tables 8 & 9.

Table 8 – Study CL2-005 - SBP - Superiority of Perindopril 3.5 mg/Amlodipine 2.5 mg as Compared to Placebo, Perindopril 3.5 mg, and Amlodipine 2.5 mg

Supine SBP (mmHg) Mean ± SD	**Per 3.5/Aml 2.5** N=246	**Placebo** N=248	**Per 3.5** N=268	**Aml 2.5** N=270
Baseline Value	161.8 ± 7.5	161.0 ± 7.4	161.4 ± 7.7	161.2 ± 7.6
End Value*	139.9 ± 13.8	146.7 ± 15.4	145.1 ± 16.5	145.1 ± 15.5
Change from baseline	-22.0 ± 14.0	-14.2 ± 16.1	-16.3 ± 17.0	-16.0 ± 15.3
Estimated Difference (1)		-7.22	-5.01	-5.20
[95% CI](2)		[-9.60; -4.84]	[-7.35; -2.67]	[-7.53; -2.87]
p-value(3)		p < 0.001	p < 0.001	p < 0.001

Table 9 – Study CL2-005 - DBP - Superiority of Perindopril 3.5 mg/Amlodipine 2.5 mg as Compared to Placebo, Perindopril 3.5 mg, and Amlodipine 2.5 mg

Supine DBP (mmHg) Mean ± SD	**Per 3.5/Aml 2.5** N=246	**Placebo** N=248	**Per 3.5** N=268	**Aml 2.5** N=270
Baseline Value	100.7 ± 4.0	100.5 ± 3.9	100.7 ± 4.0	100.6 ± 4.0
End Value*	87.1 ± 9.0	91.2 ± 9.2	91.0 ± 10.1	90.3 ± 9.8
Change from baseline	-13.6 ± 9.2	-9.3 ± 9.2	-9.7 ± 9.9	-10.3 ± 9.7
Estimated Difference (1)		-4.12	-3.64	-2.97
[95% CI](2)		[-5.63 ; -2.61]	[-5.12 ; -2.16]	[-4.45 ; -1.49]
p-value(3)		p < 0.001	p < 0.001	p < 0.001

Superiority tests of Per 3.5/Aml 2.5 as compared to reference treatment (Placebo, Per 3.5, Aml 2.5); One-sided type I error rate: 0.025

(1) Estimate of the difference between baseline and centre adjusted treatment group means: Per 3.5/Aml 2.5 minus reference treatment

(2) 95% Confidence interval of the estimate

(3) General linear model with baseline as covariate and centre as random factor

** For patients with a last post-baseline value not under treatment but with a post-baseline value under treatment, the last post-baseline value under treatment was taken into account*

Aml: Amlodipine; CI: Confidence interval; DBP: Diastolic blood pressure; Per: Perindopril; SD: Standard deviation

Perindopril 3.5 mg/amlodipine 2.5 mg was non inferior to perindopril 5 mg and amlodipine 5 mg administered separately on reducing SBP/DBP: estimate of the difference of SBP/DBP reduction between treatments was -2.8/-2.6 mmHg, in comparison to perindopril 5 mg (p<0.001 for both) and -0.3/-0.8 mmHg in comparison to amlodipine 5 mg (p≤0.003 for all). See results summarized in Tables 10 & 11.

Perindopril 3.5 mg/amlodipine 2.5 mg presented a better controlled rate than perindopril 5 mg (43.5% versus 33.3%, p=0.018, 95% CI÷[1.8; 18.5]) and a trend toward a better controlled rate than

amlodipine 5 mg (43.5% versus 37.9%, p=0.202, 95% CI÷[-3.0 ; 14.1]).

Table 10 – Study CL2-005 – SBP – Non inferiority of Perindopril 3.5 mg/Amlodipine 2.5 mg as Compared to Perindopril 5 mg and Amlodipine 5 mg

Supine SBP (mmHg) Mean ± SD	Per 3.5/Aml 2.5 N=246	Per 5 N=270	Aml 5 N=261
Baseline Value	161.8 ± 7.5	160.7 ± 7.3	162.3 ± 7.5
End Value*	139.9 ± 13.8	142.5 ± 15.0	140.5 ± 14.3
Change from Baseline	-22.0 ± 14.0	-18.2 ± 14.8	-21.8 ± 15.4
Estimated Difference (1)		-2.78	-0.29
[95% CI] (2)		[-5.11; -0.45]	[-2.64; 2.06]
p value (3)		p < 0.001	p = 0.003

Aml: Amlodipine; CI: Confidence interval; Per: Perindopril; SBP: Systolic blood pressure; SD: Standard deviation

Table 11 – Study CL2-005 - DBP - Non inferiority of Perindopril 3.5 mg/Amlodipine 2.5 mg as Compared to Perindopril 5 mg and Amlodipine 5 mg

Supine DBP (mmHg) Mean ± SD	Per 3.5/Aml 2.5 N=246	Per 5 N=270	Aml 5 N=261
Baseline Value	100.7 ± 4.0	100.1 ± 4.1	100.6 ± 4.0
End Value*	87.1 ± 9.0	89.6 ± 9.9	88.0 ± 8.7
Change from Baseline	-13.6 ± 9.2	-10.5 ± 9.7	-12.6 ± 8.9
Estimated Difference (1)		-2.59	-0.76
[95% CI] (2)		[-4.07 à -1.11]	[-2.25 à 0.73]
p value (3)		p < 0.001	p < 0.001

Non-inferiority tests of Per 3.5/Aml 2.5 as compared to reference treatment (Per 5, Aml 5); Non-inferiority limit: 2 mmHg for DBP -3 mmHg for SBP; One-sided type I error rate: 0.025

(1) Estimate of the difference between baseline and centre adjusted treatment group means: Per 3.5/Aml 2.5 minus reference treatment

(2) 95% Confidence interval of the estimate

(3) General linear model with baseline as covariate and centre as random factor

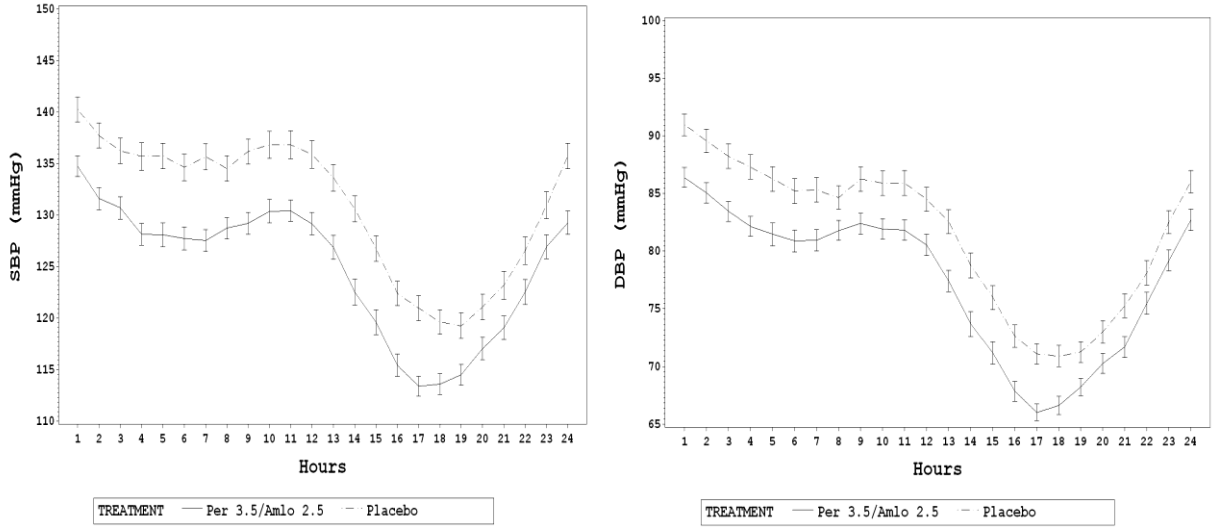
** For patients with a last post-baseline value not under treatment but with a post-baseline value under treatment, the last post-baseline value under treatment was taken into account*

Aml: Amlodipine; CI: Confidence interval; DBP: Diastolic blood pressure; Per: Perindopril; SD: Standard deviation

There were 1297 patients (among the 1581 randomized patients from the CL2-005 study) who participated in the sub-study on ambulatory blood pressure monitoring (ABPM). Results of the ABPM sub-study were consistent with those of the main study. The SBP and DBP lowering effect of the perindopril 3.5 mg/amlodipine 2.5 mg combination was statistically significantly greater over the 24-hour period than that of placebo, Perindopril 3.5 mg, Perindopril 5 mg, Amlodipine 2.5 mg and similar to Amlodipine 5 mg.

Figure 1 displayed below illustrates the efficacy of the Perindopril 3.5 mg/Amlodipine 2.5 mg fixed dose combination over placebo during the overall 24-h period at week 8.

Figure 1 – Study CL2-005 – ABPM - Hourly Means of SBP/DBP (mmHg) at Week 8 (N=1073)



PATH Study

Treatment with the fixed dose combination perindopril arginine 14 mg/amlodipine 10 mg produced mean blood pressure reductions of 22.8/15.4 mmHg SBP/DBP, compared to 18.8/12.9 mmHg for amlodipine 10 mg, and 12.7/9.1 mmHg for perindopril erbumine16 mg (corresponding to perindopril arginine 20 mg). Treatment with perindopril arginine 14 mg/amlodipine 10 mg resulted in significantly and clinically greater SBP (-4.0 mmHg vs amlodipine 10 and -10.1 mmHg vs perindopril erbumine 16 mg) and DBP (-2.5 mmHg vs amlodipine 10 and -6.3 mmHg vs perindopril erbumine 16 mg) reductions ($p<0.001$ and $p< 0.01$ respectively) and significantly higher control rates (51%) (defined as SBP/DBP < 140/90 mmHg for non-diabetics and < 130/80 mmHg for diabetics) compared to amlodipine 10 mg (37%, $p=0.001$) and perindopril erbumine16 mg (26%, $p<0.001$).

See results summarized in Tables 12, 13.

Table 12 – PATH study-Change from Baseline in Systolic Blood Pressure (mmHg)

SBP	PERa 14/Aml 10 (N=271)	PERe 16 (N=274)	Aml 10 (N=275)
Baseline Value (Mean ± SD)	157.5 ± 11.9	157.5 ± 11.4	158.0 ± 11.8
Value at Day 42 (Mean ± SD)	134.1 ± 13.5	144.1 ± 15.7	138.4 ± 13.4
Change from Baseline (LS Mean ± SE) *	-22.8 ± 0.98	-12.7 ± 0.98	-18.8 ± 0.98
Difference (*vs* PERa 14/Aml 10)		-10.1	-3.9
95% CI		[-12.6 ; -7.6]	[-6.4 ; -1.5]
p-value		<0.0001	0.0017

** Least squares mean change was based on an analysis of covariance model while controlling for treatment, baseline diastolic blood pressure, type 2 diabetes status and race*
CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.

Aml: Amlodipine; CI: Confidence interval; LS: Least square; PERa: Perindopril arginine; PERe: Perindopril erbumine; SBP: Systolic blood pressure; SD: Standard deviation; SE: Standard error

Table 13– PATH Study-Change from Baseline in Diastolic Blood Pressure (mmHg)

DBP	PERa 14/Aml 10 (N=271)	PERe 16 (N=274)	Aml 10 (N=275)
Baseline Value (Mean ± SD)	100.6 ± 4.6	100.8 ± 4.9	100.5 ± 4.8
Value at Day 42 (Mean ± SD)	85.0 ± 8.6	91.4 ± 9.7	87.2 ± 8.4
Change from Baseline (LS Mean ± SE) *	-15.4 ± 0.56	-9.1 ± 0.56	-12.9 ± 0.56
Difference (*vs* PERa 14/Aml 10)		-6.3	-2.5
95% CI		[-7.67; -4.9]	[-3.9; -1.1]
p-value		<0.0001	0.0005

**Least squares mean change was based on an analysis of covariance model while controlling for treatment, baseline diastolic blood pressure, type 2 diabetes status and race.*
Aml: Amlodipine; CI: Confidence interval; LS: Least square; PERa: Perindopril arginine; PERe: Perindopril erbumine; SBP: Systolic blood pressure; SD: Standard deviation; SE: Standard error

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Perindopril arginine
The toxicological evaluation of perindopril arginine is based on the overall toxicology profile of the erbumine salt of perindopril. No carcinogenicity, reproductive and developmental toxicity studies have been conducted with perindopril arginine

General Toxicology:
Chronic Toxicity Studies
Repeated oral gavage administration of the arginine salt of perindopril for 4 weeks in Wistar rats and Beagle dogs did not elicit unexpected toxicity in comparison with the known effects of the erbumine salt.

Carcinogenicity:
No evidence of carcinogenicity was observed in the two 104-week studies in $B_6C_3F_1$ mice and Fischer 344 rats treated with perindopril erbumine at dosages ≤6 times the maximum recommended human dose (MRHD).

Genotoxicity:
The genotoxic potential of perindopril arginine was investigated in a series of *in vitro* and *in vivo* tests tabulated below.

In vitro

Test	Concentration (mcg perindopril free acid/plate)	Conclusion
Detection of reverse mutation in histidine-requiring *Salmonella typhimurium* and tryptophan-requiring *Escherichia coli* (Ames test)		
Salmonella typhimurium (TA100, TA1535, TA1537 and TA98) and *Escherichia coli (WP2 (pKM101) and WP2 uvrA (pKM101)*	50 150 500 1500 5000 in the presence and absence of S9 mix	No significant, reproducible or concentration-related increase in the number of revertant colonies was seen at any tested concentrations of perindopril arginine, with and without metabolic activation by preincubation of direct plating assay with any strain. Under the conditions of the study, perindopril arginine salt was considered to be devoid of mutagenic potential.
Mutation of the thymidine kinase (tk) locus of mouse lymphoma assay on L5178Y cells (MLA)		
Mouse lymphoma cells L5178Y	0 112.5 225 450 900 1800 3685 in the presence and absence of S9	When tested up to 10mM, Perindopril arginine salt did not induce mutation at the tk locus of L5178Y mouse lymphoma cells in two independent experiments, in the absence and presence of S9. It was concluded that, under the conditions employed in this study, Perindopril arginine salt is not mutagenic in this test system in the absence and presence of S9.
Induction of chromosome aberrations in cultured human peripheral blood lymphocytes		
Primary human lymphocytes from the pooled blood of three healthy male volunteers	1887 2358 3685 in the presence and absence of S9	It was concluded that perindopril arginine induced chromosome aberrations in cultured human peripheral blood lymphocytes. The effect was restricted to prolonged exposure in the absence of S9. Mitotic accumulation and the effects of the test article on chromosome morphology meant that following prolonged (20 hour) exposure, shortening of the chromosomes, mitotic accumulation and chromosomes aberrations were observed. In these instances, it was not possible to accurately assess toxicity at concentrations selected for chromosome aberration analysis, making interpretation of the biological significance of the data difficult to assess. It was considered that a meaningful selection of concentrations to be analysed for chromosome aberrations could not be made for this phase of the study.

In vivo

Species (+age at the beginning of	Number of animals	Route of administration	Concentration (mg perindopril free acid/kg)	Major investigations	Conclusion

the treatment)					
Micronucleus cytogenic assay in mice bone marrow after oral administration					
Mouse/Swiss (OF1) (8 weeks)	4 groups of 6 to 12 per gender	Oral gavage	0 500 1000 2000	General toxicity Plasma levels Acceptability of the study Evaluation of genotoxicity	No statistically significant or dose-related increase in the number of micronucleated polychromatic erythrocytes versus negative controls was seen in the animals dosed with perindopril arginine salt. Under the conditions of this study, Perindopril arginine salt was devoid of clastogenic potential.

No mutagenic or clastogenic potential was found in the Ames test, in the mouse lymphoma assay, in the chromosomal aberration test or in the bone marrow micronucleus assay ≤2000 mg perindopril free acid/kg. Chromosomal aberrations were found after prolonged (20 hours) treatment of human lymphocytes with 1294 µg perindopril free acid/mL, but the test was considered inappropriate since the accurate assessment of toxicity was not possible. The absence of clastogenic effect *in vitro* after more prolonged exposure (24 hours) to higher concentrations (≤3685 µg perindopril free acid/mL) in the mouse lymphoma assay, combined with the absence of clastogenic potential *in vivo* after one administration ≤2000 mg perindopril free acid/kg, supported the overall non genotoxicity potential of perindopril arginine salt.

Reproductive and Developmental Toxicology:

Fertility Studies

Studies were performed by administrating perindopril erbumine by the oral route. In the table below, the reported doses or concentrations of perindopril are expressed in terms of perindopril erbumine salt.

Species	Number of Animals/ Group	Dosage mg/kg/day	Administration Route	Information
Rat (Wistar)	12 M + 24 F	0, 1, 3, 10 M: 80 days before mating to sacrifice. F: 14 days before mating to PR7	PO	Males: Reduction in growth with no disturbance of the reproductive function. Mean weight gain relative to the control group was -30%, -36%, -35% for the 1, 3, 10 mg/kg/day groups respectively. Females: Reduction in growth at the high dose. During treatment before mating, mean weight gain relative to the control group ranged between -10% to -26%. Over the period of gestation during which the treatment was administered the mean weight gain relative to control was -23%, -21% and -48% in the 1, 3 and 10 mg/kg/day groups respectively. Reduction in the number of ovules produced in the three groups. The mean number of corpora lutea ranged between 9.4 (-15% relative to the control group) and 10.0 (-9.9%).

				No abnormality related to the migration of the egg, its implantation or embryonic and fetal development was demonstrated.
Rat (Wistar)	30 M + 30F	0, 1, 2, 4 M: 80 days before mating to sacrifice. F: 14 days before mating to PR20 or up to parturition	PO	Growth in the animals was retarded. Fertility of males (100%, 93% and 90% in the 1, 2, 4 mg/kg/day groups respectively versus 97% in the control group) and libido of females were reduced at the intermediate and high doses (the percentage of effective mating of the GO female breeders in the 2 higher dose groups was 0.97 and 0.93 respectively versus 1.0 in the control group). There was no effect on the fertility of females. The fetus of dams treated with the high dose presented an increased frequency of dilatation of the renal pelvis (2.0%, 2.5% and 7.1% in the 1, 2, 4 mg/kg/day groups respectively, versus 3.3% in the control group) and delayed ossification of the sternum (18%, 20%, 38% in the 3 treated groups respectively), though there was no teratogenic effect. The mortality of the G_1 pups was increased at the high dose (The mortality at birth was not alterated by the treatment. It was 0% in the lower dose groups and 1.7% in the higher dose group versus 0% in controls. The mortality between D1 and D21 of lactation was 0%, 1.8%, 5.4% in the 1, 2, 4 mg/kg/day groups respectively, versus 3.6% in the control group) and their growth and physical development were retarded. These changes did not affect the reproductive capacity of the G_1 generation, the gestation of the G_1 females and the characteristics of the G_2 pups.

PR (n) = nth day of pregnancy; G = generation; D = day

Teratogenicity Studies

Studies were performed by administrating perindopril erbumine by the oral route. The following doses or concentrations are expressed in terms of perindopril erbumine salt.

Species	Number of Animals/ Group	Dosage mg/kg/day	Administration Route	Information

Mice (NMRI)	Between 31 and 37 inseminated F	0, 1, 4.5, 20 From PR6 to PR15	PO	Apart from a slight, though non significant reduction in body weight of the dams treated with the high dose between the 6th and 15th days of gestation (relative to the control group: -14.9%), no abnormality, in particular, no embryotoxicity or teratogenicity were observed.
Rat (Wistar)	25 treated F	0, 1, 4, 16 From PR6 to PR7	PO	Dams: increase in water consumption.(during the first week of treatment, the mean increase was +4.0, +5.0 and +3.9 g/day for the 1, 4, 16 mg/kg/day groups treatment respectively, i.e. +567%, +733%, +550% relative to the control group ; during the second week of treatment, the increase in water consumption was +39%, +42% and + 165% relative to the control group in the 3 treated groups respectively). The in-utero development of the fetus was unchanged though there was a higher incidence of hydronephrosis which appeared to be dose dependent (2 cases in the low and intermediate doses, 5 in the high dose) and a delayed ossification in the high group only (i.e. 11.5%, 15.5%, 21.1% in the 3 treated groups respectively, versus 11.6% in the control group). No sign of teratogenicity.
Rabbit (New Zealand)	Control C1: 18 F Control C2: 27 F treated: 18 F 27 F 24 F	Drink water without NaCl: 0 Drink water with 0.9% NaCl: 0 0.5 1.5 5.0 From PR6 to PR18	PO	Under these conditions, there was no maternal toxicity or any embryotoxic or teratogenic effect on the fetuses. A slight increase in post-implantation losses at the highest dose (i.e. 21.2% versus 11% in the control group) was seen.
Monkey (cynomolgus)	10 F pregnant 12 F pregnant 12 F pregnant 12 F pregnant	0 1 4 16 From PR 20 to PR 50	PO	2 animals in each group died following episodes of diarrhea. At 16 mg/kg, maternal toxicity resulted in a reduction in the water consumption (-45% relative to the control group), during the treatment period. Nevertheless, no adverse effects on the fetuses were noted.

PR (n) = nth day of pregnancy

No teratogenic effects of perindopril were seen in studies of pregnant rats, mice, rabbits and cynomolgus monkeys.

Amlodipine

Carcinogenicity:

There was no evidence of a carcinogenic effect when amlodipine was administered in the diet for ≤24 months to rats and at doses of ≤2.5 mg/kg/day in mice.

Perindopril arginine/Amlodipine combination

General Toxicology:

The safety profile of the perindopril/amlodipine combination was assessed in Wistar rats (n=10/sex/group) by daily gavage for 13 weeks at 3.75 mg/2 mg, 7.5 mg/4 mg, 15 mg/8 mg, 15 mg/0 mg or 0 mg/8 mg/ per kg. No mortality occurred in this study. At the end of the study, a lower mean

bodyweight was noted for the males given amlodipine at 8 mg/kg either alone (-10% *versus* control, p<0.01) or in combination with perindopril at 15 mg/kg (-7% versus control, not significant).

Lower mean ratios of heart weights to body weight were seen for the males given perindopril either in combination with amlodipine at 3.75 mg/2 mg, 7.5 mg/4 mg and 15mg/8 mg per kg dosages (-9%, -11% and -12% versus control, respectively, p<0.01 for all) or alone at 15 mg/kg
(-14% versus control, p<0.01). For the females, lower mean ratios of heart weight to body weight were seen only for those given perindopril alone at 15 mg/kg (-8% versus control, p<0.05).

These isolated abnormalities are considered of minor toxicological importance, given that the high safety margin dose around 12 up to 50 times MRHD.

Neither new target organ toxicity nor relevant additive effects were identified with the combination of perindopril/amlodipine. The No Observed Adverse Effect Level (NOAEL) was set at 7.5 mg/4 mg/ per kg of perindopril arginine/amlodipine.

DETAILED PHARMACOLOGY

Perindopril arginine and amlodipine have complementary mechanisms of action which could account for potential synergistic pharmacological effects. Perindopril inhibits the renin angiotensin system, amlodipine induces a peripheral arterial dilation leading to a plasma renin activity increase. Perindopril inhibits the secretion of aldosterone and inhibits reabsorption of sodium on the proximal renal tubule.

Perindopril

In Vitro Studies:
Perindopril was shown to be an inhibitor of angiotensin converting enzyme (ACE) in both plasma and tissue. Perindoprilat, the diacid form of perindopril, exhibited greater inhibition of ACE activity than perindopril (IC_{50} = 2 x 10^{-9}M and 800 x 10^{-9}M respectively).

In Vivo Studies:
The mechanism of action of perindopril was previously established with the market authorization of COVERSYL® (perindopril erbumine). Perindopril erbumine at dose of 4 mg daily is equivalent to 5 mg/day perindopril arginine.

Following oral dosing of perindopril to normotensive (0.03 to 1 mg/kg) or hypertensive (0.3 to 3 mg/kg) rats, plasma ACE inhibition was assessed *in vivo* by the decrease in pressor response to intravenous angiotensin I. Orally administered to conscious dogs, perindopril produced a dose-dependent reduction (34% at 0.1 mg/kg, 60% at 0.3 mg/kg and 92% at 1 mg/kg) of angiotensin I (150 ng/kg IV) pressor response but had no effect on angiotensin II (100 ng/kg IV) response. In normotensive rats, plasma ACE was maximally inhibited (≥ 90%) by perindopril (1, 4 or 8 mg/kg p.o.) 1 hour following administration, then returned to control levels 24 hours later.
After 4 weeks of oral treatment (10 mg/kg) in stroke-prone spontaneously hypertensive rats, converting enzyme inhibition was mostly demonstrated in kidney (96%), aorta (64%), heart (52%), lung (36%) and brain (26%).
In human subjects, perindopril at single oral doses of 4 to 8 mg/day produced 80% inhibition of plasma

ACE activity between 2 and 8 hours post-dose, with 40 to 60% inhibition persisting at 24 hours post-dose. Multiple oral doses of perindopril over 7 days (4 to 8 mg/day) confirmed the inhibitory effect on plasma ACE and showed that it produces corresponding decreases in angiotensin II with significant increases in plasma renin activity.

Amlodipine

Cardiovascular Activity - *In Vivo*:
In anesthetized dogs, amlodipine (i.v. 25-1600 µg/kg) was a potent coronary and peripheral vasodilator; ED50 values were 103 and 212 µg/kg for reductions of coronary and systemic vascular resistances, respectively. The reductions in vascular resistance were associated with corresponding increases in cardiac output, coronary flow, heart rate and myocardial contractility. Amlodipine possessed slow onset of action, minimal effect on blood pressure, and a long duration of action. Amlodipine caused slight, transient negative inotropic responses only at the highest dose, in excess of that required to cause maximal vasodilatation. The drug did not adversely affect atrial ventricular conduction, as assessed by PR interval.

Oral administration of amlodipine (0.5 to 2.0 mg/kg) to conscious dogs produced dose-related reductions in systemic vascular resistance (max. of 78%) and reflexly-induced increases in heart rate, cardiac output and myocardial contractility; maximum effects were achieved much later (3 to 5 hours) than after parenteral administration (5 to 30 min) which may explain the dose-related modest blood pressure reductions (max. change of 25%) observed by the oral route.

Antihypertensive Efficacy - *In Vivo*:
Amlodipine produced dose-related reductions in blood pressure of spontaneously hypertensive rats (SHR) after oral administration. The antihypertensive effect was maintained for ≥6 h after each one of the 3 doses used (1, 3, and 10 mg/kg). In young SHR the development of hypertension was attenuated by 60% over a 12-week period when amlodipine was added to the diet to provide the dose of 8 mg/kg/day. In mature SHR receiving amlodipine for 8 weeks, a marked antihypertensive effect was evident by day 2 and attained a maximum by day 5. This effect was maintained for the remaining treatment period with no change in heart rate. In addition, treated animals showed a small, but statistically significant, reduction in ventricular weight and marked elevation in plasma renin activity.

In conscious renal-hypertensive dogs, oral administration of single doses of amlodipine (0.25, 0.5 and 1.0 mg/kg) produced dose-related reductions in blood pressures with maximum effects occurring at 5 hours post-dose. These responses were accompanied by dose-related increases in heart rate.

The slow onset and long-lasting antihypertensive effects of amlodipine were confirmed in conscious renal-hypertensive dogs in which blood pressure was recorded continuously for 24 hours.

In conscious renal-hypertensive dogs, orally administered amlodipine (0.025, 0.05 and 0.25 mg/kg/day) for 10-14 days produced progressive reductions in the daily, resting, pre-dose blood pressure which stabilized after 4 or 5 days. The minimum blood pressures achieved each day were approximately equivalent and tolerance did not develop. Heart rate was inconsistently affected.

For more detailed pharmacology on amlodipine, please refer to the Product Monograph for NORVASC.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr VIACORAM®

Perindopril arginine and amlodipine (as amlodipine besylate) tablets

Read this carefully before you start taking **VIACORAM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VIACORAM**.

Serious Warnings and Precautions

- VIACORAM should not be used during pregnancy. Taking VIACORAM during pregnancy can cause injury or even death to your baby.
- If you discover that you are pregnant while taking VIACORAM, stop the medication and talk to your healthcare professional as soon as possible.

What is VIACORAM used for?

VIACORAM is used in adults, aged 18 to 65, to treat mild to moderate **high blood pressure**.

How does VIACORAM work?

VIACORAM contains 2 medicines, perindopril arginine and amlodipine. They work together to control your blood pressure.

- Perindopril arginine belong to a class of medicines called angiotensin converting enzyme (ACE) inhibitors. You can recognize ACE inhibitors because their medicinal ingredient ends in '-PRIL'. It works by relaxing the blood vessels so blood can flow more easily.
- Amlodipine is a calcium channel blocker. It also works by relaxing the blood vessels.

This medicine does not cure your high blood pressure. It helps to control it. Therefore, it is important to continue taking VIACORAM regularly even if you feel fine. Do not stop taking your medicine without talking to your healthcare professional.

What are the ingredients in VIACORAM?

Medicinal ingredients: perindopril arginine and amlodipine (as amlodipine besylate)

Non-medicinal ingredients: colloidal anhydrous silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose

VIACORAM comes in the following dosage forms:

tablets: 3.5 mg /2.5 mg, 7 mg / 5 mg, 14 mg / 10 mg.

Do not use VIACORAM if you:

- are allergic to:
    - perindopril
    - amlodipine
    - other ACE inhibitors
    - medicines of the dihydropyridine type (a type of calcium channel blocker, also used to lower blood pressure)
    - any non-medicinal ingredient in VIACORAM (see **What are the ingredients in VIACORAM?**)
- have had an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing:
    - to any other ACE inhibitor
    - where the reason is not known (idiopathic angioedema)
- have been diagnosed with hereditary angioedema (an increased risk of getting an allergic reaction that is passed down in families)
- are taking a medicine for heart failure containing sacubitril/valsartan. Taking VIACORAM with sacubitril/valsartan increases the risk of serious allergic reaction (angioedema). You must wait at least 36 hours after your last dose of sacubitril/valsartan before starting VIACORAM.
- have kidney problems, such as:
    - a narrowing of the blood vessels to one or both kidneys (renal artery stenosis)
    - you are on dialysis or receive any other type of blood filtration. Depending on the machine that is used, VIACORAM may not be suitable for you.
- are already taking a blood pressure-lowering medicine that contains aliskiren and you have diabetes or kidney disease
- have heart problems, such as:
    - aortic stenosis, a narrowing of the aortic heart valve
    - problems with the heart muscle (hypertrophic cardiomyopathy)
    - heart failure
- are pregnant or planning to become pregnant. Taking VIACORAM during pregnancy can cause injury and even death to your baby.
- are breastfeeding. VIACORAM passes into breast milk.
- are lactose intolerant or have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in VIACORAM.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VIACORAM. Talk about any health conditions or problems you may have, including if you:

- are allergic to any drug used to lower blood pressure
- are of African origin
- have a severe increase in blood pressure (hypertensive crisis)
- have low blood pressure
- are taking any of the following medicines:
    - other blood pressure lowering medicines, such as:

        - aliskiren
        - an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN".
        - other ACE inhibitors
    - anti-cancer or medicines used to prevent organ rejection after a transplant such as temsirolimus, everolimus, sirolimus, cyclosporine
    - non-steroidal anti-inflammatory drugs, used to treat pain and inflammation
    - medicines used to manage diabetes (dipeptidyl peptidase IV (DPP-IV) inhibitors). You can recognize a DPP-IV inhibitor because its medicinal ingredient ends in "-GLIPTIN.
    - medicines containing a neutral endopeptidase inhibitor (e.g., sacubitril) to treat heart failure
    - allopurinol, used to treat gout
    - procainamide, used to treat irregular heartbeat
- have diabetes, heart, liver or kidney problems (including kidney transplantation)
- are on dialysis
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating
- are at risk for developing high levels of potassium in your blood (hyperkalemia). This can be serious and can happen if you are taking:
    - a salt substitute that contains potassium
    - potassium supplements
    - a kind of "water pill" (potassium sparing) that makes your body hold on to potassium
    - other medicines that may increase potassium in your blood, such as the blood thinner heparin or trimethoprim or sulfamethoxazole, antibiotics used to treat bacterial infections
- are on a low-salt diet
- have systemic lupus erythematosus (SLE), an autoimmune disease that can affect many parts of the body
- have a skin condition known as scleroderma or "hard skin" (thickening of the skin)
- have recently received or are planning to get allergy shots for bee or wasp stings
- have a condition in which your body releases too much of the hormone aldosterone in your blood (primary aldosteronism)
- are on LDL Apheresis (a treatment to lower the LDL cholesterol in the blood)
- are receiving gold (sodium aurothiomalate) injections

Other warnings you should know about:

VIACORAM can cause serious side effects, including:

- **Allergic reaction / Angioedema**: Allergic reactions (angioedema) causing swelling of tissues under the skin, sometimes affecting the face and throat, have happened in people taking VIACORAM. These allergic reactions may happen at any time during treatment with VIACORAM and can be life threatening. Very rarely, cases have been fatal. If you experience an allergic reaction, stop taking VIACORAM and get immediate medical help.
- **Hypotension (low blood pressure):** You may feel dizzy or light-headed:
    - in the first few days after you start taking VIACORAM
    - when your dose is increased
    - when you exercise
    - when the weather is hot

You should lie down if this happens. If you faint, stop taking VIACORAM and talk to your healthcare professional.

- **Blood disorders**: ACE inhibitors, such as VIACORAM, may cause:
  - neutropenia / agranulocytosis (decrease in white blood cells)
  - thrombocytopenia (low blood platelets)
  - anaemia (low red blood cells)
- **Hypoglycemia (low blood sugar**): VIACORAM may cause low blood sugar in patients with:
  - diabetes who are taking oral antidiabetic medicines or insulin
  - kidney problems

  You should closely monitor your blood sugar level, especially during the first month of your treatment with VIACORAM.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Increased sensitivity of the skin to sun: Your skin may become sensitive to the sun while you are taking VIACORAM. Limit your exposure to the sun and to indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside. Talk to your healthcare professional if your skin gets itchy and red after being exposed to sunlight.

Cough: You may develop a dry and persistent cough while taking VIACORAM. This usually goes away once you stop taking VIACORAM or when the dose is lowered. Tell your healthcare professional if you experience this symptom.

Blood tests: Your healthcare professional may do blood tests before you take VIACORAM and/or during treatment. These tests may check:

- the level of red and white blood cells and platelets in your body
- that your liver or kidneys are working properly
- the potassium levels in your blood

Surgery: Before surgery or general anesthesia (even at the dentist's office), tell your healthcare professional that you are taking VIACORAM. You may experience a sudden fall in blood pressure when you are under general anesthesia.

Driving and using machines: Before you perform tasks, which may require special attention, wait until you know how you respond to VIACORAM. Dizziness, headache, fatigue, nausea, weariness or fainting can occur, especially after the first dose and when the dose is increased.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VIACORAM.

- medicines that lower your blood pressure. These include:
  - diuretics ("water pills")
  - aliskiren-containing medicines
  - angiotensin receptor blockers (ARBs)
  - other ACE inhibitors
  - calcium channel blockers

- medicines that can increase the levels of potassium in your blood. These include:
    - salt substitutes that contains potassium
    - potassium supplements
    - potassium-sparing medicines, such as spironolactone, eplerenone, triamterene, amiloride
    - heparin, used to thin the blood and prevent blood clots
    - medicines affecting the immune system, such as cyclosporine, tacrolimus
    - other medicines that may increase serum potassium, such as the antibiotics trimethoprim and sulfamethoxazole
- medicines used to treat diabetes. These include:
    - insulin
    - metformin and other oral medicines
    - a class of medicine called DPP-IV inhibitors such as sitagliptin, linagliptin, saxagliptin
- allopurinol, used to treat gout
- dextran sulphate, used to treat life-threatening low blood pressure
- lithium used to treat bipolar disorder
- a class of medicines called nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling, such as ASA, ibuprofen, naproxen, celecoxib
- a class of medicines called vasodilators, including nitrates, such as nitroglycerin, used to treat chest pain
- procainamide used to treat irregular heartbeats
- medicines to treat mental health problems such as depression, anxiety and schizophrenia, such as tricyclic antidepressants, antipsychotics, imipramine-like antidepressants, neuroleptics
- medicines that suppress the immune system, such as ciclosporin, tacrolimus
- medicines used to treat low blood pressure, shock and asthma, such as ephedrine, noradrenaline, adrenaline
- baclofen, used to treat muscle stiffness in diseases such as multiple sclerosis
- antibiotics, used to treat bacterial infections, such as rifampicin, erythromycin, clarithromycin
- medicines used to treat epilepsy, such as carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone
- medicines used to treat fungal infections, such as itraconazole, ketoconazole
- alpha-blockers used for the treatment of enlarged prostate such as prazosin, alfuzosin, doxazosin, tamsulosin, terazosin
- corticosteroids used to treat inflammation
- gold salts, especially when given intravenously, used to treat rheumatoid arthritis
- medicines used to treat HIV/AIDS, such as ritonavir, indinavir, nelfinavir
- estramustine, used to treat prostate cancer
- St John's wort, an herbal medicine used to treat depression
- simvastatin, used to lower cholesterol
- treatment for bee and wasp allergies
- tetracosactide, used as a diagnostic agent
- medicines containing neutral endopeptidase (NEP) inhibitors, such as sacubitril, available in combination with valsartan, used to treat heart failure
- a class of medicines called mTOR inhibitors, used to prevent organ rejection, such as sirolimus, everolimus, temsirolimus
- grapefruit or grapefruit juice

How to take VIACORAM:

- Take VIACORAM:
  - exactly as prescribed
  - at the same time each day, preferably **in the morning**, before a meal
  - swallowed whole, with water

Usual dose:

Your healthcare professional will decide on the dose that is right for you based on your needs.

Overdose:

If you think you, or a person you are caring for, have taken too much VIACORAM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose during the day, take the next one at the usual time. Do not double dose.

What are possible side effects from using VIACORAM?

These are not all the possible side effects you may have when taking VIACORAM. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- cough (often described as dry and irritating, usually is worse at night or when lying down)
- headache
- stomach pain
- diarrhea, nausea
- changes in bowel habits
- change in weight (increase or decrease)
- dry mouth, abnormal taste
- dizziness, vertigo (feeling of spinning)
- tiredness, fatigue, drowsiness
- trouble sleeping
- rash, itching
- increased sweating
- flushing
- tingling of the skin, pins and needles sensation
- back pain, muscle pain, joint pain

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Edema (swelling of the hands, ankles or feet caused by too much fluid building up inside the body): swollen or puffy legs or hands, feeling heavy, achy or stiff	✓		
COMMON			
Hyperkalemia (too much potassium in the blood): irregular heartbeat, muscle weakness and generally feeling unwell		✓	
Persistent Cough		✓	
UNCOMMON			
Angioedema and Severe Allergic Reaction: rash, hives, swelling of the face, hands and feet, genitals, lips, tongue or throat, difficulty swallowing or breathing, wheezing, swelling of the digestive tract causing stomach pain, diarrhea, nausea or vomiting			✓
Blood Disorders: infections, fatigue, fever, aches, pains, and flu-like symptoms, bruising, bleeding, weakness, small purple or red dots under the skin		✓	
Bronchospasm: difficulty breathing and coughing, chest tightness, wheezing or whistling sound when breathing			✓
Chest pain		✓	
Cerebrovascular accident/Stroke (bleeding or blot clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurred vision, difficulty swallowing or speaking, lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide		✓	
Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		✓	
Erectile Dysfunction: unable to get or keep an erection	✓		
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision, fatigue	✓		
Hypotension (low blood pressure): dizziness, fainting, light-headedness. May occur when you go from lying or sitting to standing up.	✓		
Kidney Problems: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		✓	
Myocardial Infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			✓
Palpitations (fast beating, fluttering or pounding heart):		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
skipping beats, beating too fast, pounding, fluttering rapidly			
Pemphigoid/Pemphigus: blisters of different sizes develop on the skin			✓
RARE			
Acute Renal Failure (severe kidney problems): confusion, itchiness or rashes, puffiness in your face and hands, swelling in your feet or ankles, urinating less or not at all, weight gain			✓
SIADH (syndrome of inappropriate antidiuretic hormone secretion): dark urine, nausea, vomiting, muscle cramps, confusion and fits (seizures)		✓	
Worsening of Psoriasis (chronic skin disease): red, itchy, scaly patches of the skin		✓	
VERY RARE			
Liver Problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heartbeat, nausea and vomiting, tenderness when touching the abdomen			✓
Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (severe skin reactions): any combination of itchy skin rash, redness, blistering and peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands, joint pain, yellowing of the skin or eyes, dark urine			✓
UNKNOWN			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Extrapyramidal Disorder: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want, tremors, involuntary facial movements			✓
Raynaud's Phenomenon (episodes of reduced blood flow): cold feeling in fingers or toes (and sometimes nose, lips and ears), prickly or stinging feeling, change in skin colour to white then blue		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of reach and sight of children.
- Store at room temperature (15-30°C). Protect from light.
- Do not use after the expiry date stated on the carton, blister or bottle.

If you want more information about VIACORAM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-

product-database.html); the manufacturer's website (www.servier.ca), or by calling 1-800-363-6093.

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