

PRODUCT MONOGRAPH

Pr **VIACORAM[®]**

Perindopril arginine and Amlodipine tablets

3.5 mg Perindopril arginine/2.5 mg Amlodipine (as amlodipine besylate)

7 mg Perindopril arginine/5 mg Amlodipine (as amlodipine besylate)

14 mg Perindopril arginine /10 mg Amlodipine (as amlodipine besylate)

Angiotensin converting enzyme inhibitor / Dihydropyridine calcium antagonist

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VIACORAM[®]
perindopril arginine and amlodipine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal 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. <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

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 [DOSAGE AND ADMINISTRATION](#) section).

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).

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.

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 [Dosage Forms, Composition and Packaging section of the product monograph](#).
- Patients with renal impairment (creatinine clearance < 60 ml/min) (see [WARNINGS and PRECAUTIONS, Renal](#)).
- Patients with a history of hereditary/idiopathic angioedema, or angioedema related to previous treatment with an ACE-inhibitor (see [WARNINGS and PRECAUTIONS, Immune](#)).
- Women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraception. (see [WARNINGS and PRECAUTIONS, Special Populations, Pregnant Women](#)).
- Nursing women (see [WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women](#)).
- 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.
- Combination with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or 2) or moderate to severe renal impairment (GFR < 60ml/min/1.73m²) (see [WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System \(RAS\) and Renal](#), and [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 [WARNINGS AND PRECAUTIONS, Sensitivity/Resistance](#)).
- Patients with extracorporeal treatments leading to contact of blood with negatively charged surfaces.
- Patients with bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney.

WARNINGS AND PRECAUTIONS

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.

General

Driving a vehicle or performing other hazardous tasks

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.

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/1.73m²). Therefore, the use of VIACORAM[®] in combination with aliskiren-containing drugs is contraindicated in these patients (see [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 [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, diarrhoea 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 ischaemic 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.

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 [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 anaemia 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 [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 [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) or neutral endopeptidase (NEP) inhibitor may be at increased risk for angioedema. Caution should be used when initiating ACE inhibitor therapy in patients already taking a mTOR, DPP-IV or NEP inhibitor or vice versa (see [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.

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 [DRUG INTERACTIONS](#)).

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 [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/1.73m²) (See [CONTRAINDICATIONS](#) and [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. 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.

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 [CONTRAINDICATIONS](#)).

Sexual 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 [TOXICOLOGY - Reproductive and developmental toxicity](#)).

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 $\leq 0.1\%$ of patients in clinical trials with amlodipine.

Special Populations

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.

Nursing Women:

The presence of ACE inhibitor in human milk has been reported. The use of VIACORAM[®] is contraindicated during breastfeeding (see [CONTRAINDICATIONS](#)).

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.

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.

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 [DRUG INTERACTIONS, Drug-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.

ADVERSE REACTIONS**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.

Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

CL2-005 study

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

presented in [Table 1](#).

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

Emergent Adverse events	Per 3.5/Aml 2.5 N = 249 n (%)	Placebo N = 251 n (%)	Per 3.5 mg N = 273 n (%)	Aml 2.5 mg N = 274 n (%)	Per 5 mg N = 272 n (%)	Aml 5 mg N = 264 n (%)
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 2](#).

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

System Organ Class Preferred Term	PERa 14/Aml 10 (N = 279) n (%)	PERe 16 (N = 278) n (%)	Aml 10 (N = 280) n (%)
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)
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

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%):

Cardiac disorders: angina pectoris, atrial fibrillation, chest pain, myocardial infarction, sinus tachycardia

Gastrointestinal disorders: constipation, diarrhea, dry mouth, vomiting

Immune system disorders: angioedema, dermatitis allergic, pruritus allergic

Investigations: creatinine renal clearance decreased, gamma-glutamyltransferase increased

Nervous system disorders: cerebrovascular accident, ischemic stroke, syncope, transient ischemic attack

Vascular disorders: hot flush, hypotension, orthostatic hypotension

Musculoskeletal and connective tissue disorders: arthralgia, muscle spasms, myalgia

Psychiatric disorders: insomnia, depression

Reproductive system and breast disorders: erectile dysfunction

Skin and subcutaneous tissue disorders: hyperhidrosis

General disorders and administration site conditions: asthenia

Blood and lymphatic system disorders: leukopenia, thrombocytopenia

Abnormal Hematologic and Clinical Chemistry Findings

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.

Post-Market Adverse Drug 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, pruritus, 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

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

Renal and urinary disorders: micturition disorder, nocturia, renal failure

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, urticarial

Vascular disorders: vasculitis

DRUG INTERACTIONS

Drug-Drug Interactions

Table 3- Established or Potential Drug-Drug Interactions

Interacting agent	Ref	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.
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.
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. VIACORAM® should be used with caution together with CYP3A4 inducers.

Interacting agent	Ref	Effect	Clinical comment
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.
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 <i>vice versa</i> (see WARNINGS AND PRECAUTIONS, General, 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 CONTRAINDICATIONS and 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.
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.
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)		Patients taking concomitant mTOR inhibitors may be at increased risk for angioedema.	Caution should be used when initiating VIACORAM [®] in patients already taking mTOR inhibitors or <i>vice versa</i> (see WARNINGS AND PRECAUTIONS, Head and Neck Angioedema).

Interacting agent	Ref	Effect	Clinical comment
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.
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 WARNINGS AND PRECAUTIONS, General, Head and Neck Angioedema).
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.

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.

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. VIACORAM® should be used with caution together with CYP3A4 inducers.

Drug-Laboratory Interactions

Interactions with laboratory products/methods have not been established.

Drug-Lifestyle Interactions

Lifestyle interactions have not been established.

DOSAGE AND ADMINISTRATION

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).

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.

Elderly:

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 [WARNINGS AND PRECAUTIONS](#)).

Renal Impairment:

VIACORAM[®] is contraindicated in patients with renal impairment (creatinine clearance <60 ml/min) (see [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 [DRUG INTERACTIONS, Drug-Drug Interactions](#)).

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.

Administration

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 [ACTION AND CLINICAL PHARMACOLOGY – Special Populations, Renal impairment](#)). 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.

ACTION AND CLINICAL PHARMACOLOGY

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 [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.

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.

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 4: 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-∞}(ng*h/mL)
Perindopril	95.4 (41%)	0.68 (0.54 – 0.88)	120 (17%)
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

Pediatrics:

No pharmacokinetic data are available in the pediatric population.

Geriatrics:

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.

Gender: The effectiveness of VIACORAM[®] was not influenced by gender.

Race:

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.

Renal impairment:

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 [CONTRAINDICATIONS, 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.

Hepatic impairment:

VIACORAM[®] is not recommended in patients with impaired liver function (see [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.

Genetic Polymorphism: Pharmacokinetics differences due to genetic polymorphism have not been studied.

STORAGE AND STABILITY

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


SPECIAL HANDLING INSTRUCTIONS


Not Applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form

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.

PART II: SCIENTIFIC INFORMATION

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

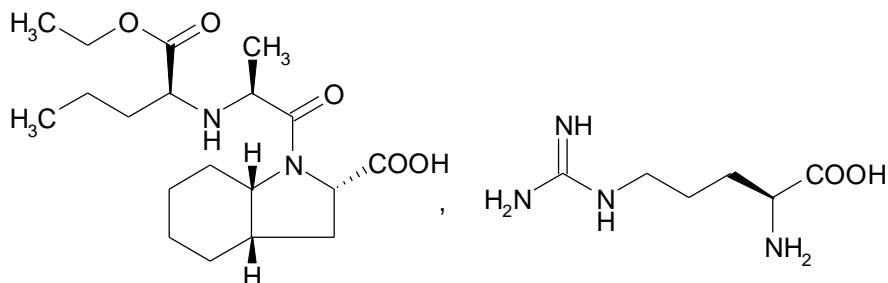
or as a synonym:

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

Molecular formula: C₁₉ H₃₂ N₂ O₅, C₆ H₁₄ N₄ O₂

Molecular weight: 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.

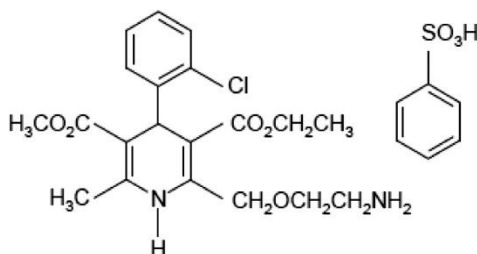
The pKa value for the NH²⁺/NH pair is 5.66, and 3.50 for the COOH/ COO⁻ pair.

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: $C_{20}H_{25}ClN_2O_5$, $C_6H_6O_3S$

Structural Formula:



Molecular Weight: 567.1

Physicochemical properties: Amlodipine besylate is a white crystalline substance.

Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol.

M.P.= 203°C with decomposition.

The pKa = 9.02 at 23.5°C.

CLINICAL TRIALS

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, $95 \text{ mmHg} \leq$ supine diastolic blood pressure (DBP) $< 110 \text{ mmHg}$ and $150 \text{ mmHg} \leq$ supine systolic blood pressure (SBP) $< 180 \text{ mmHg}$, 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/m^2 , 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 5 - Summary of Patient Demographics and Trial Design for Study CL2-005

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

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

Study results

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 6 & 7](#).

Table 6 - 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

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

Table 7- 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

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
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 8 & 9.

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 8 –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 9 - 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 ; -1.11]	[-2.25 ; 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

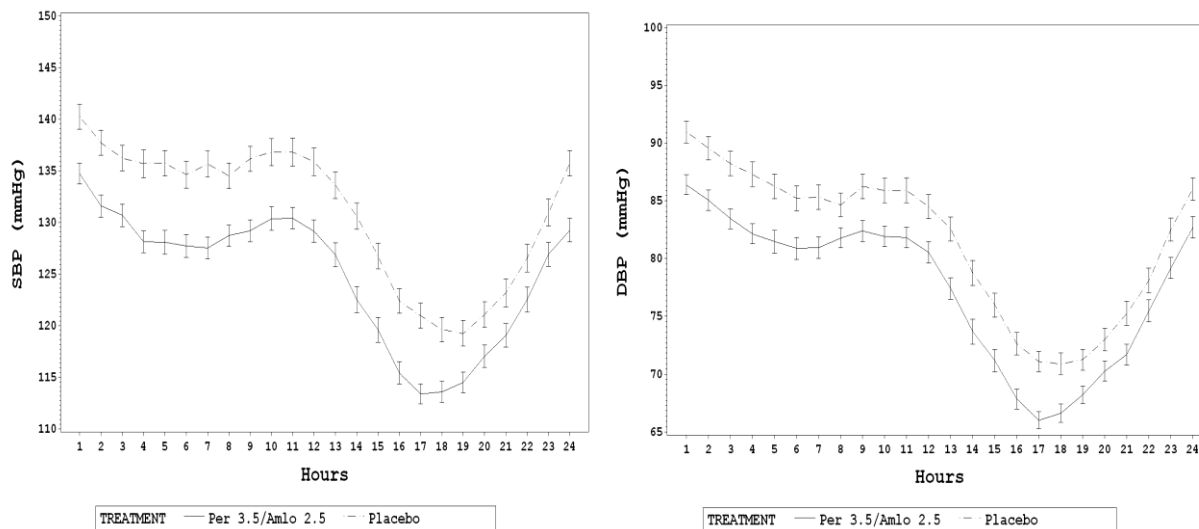
Aml: Amlodipine; CI: Confidence interval; DBP: Diastolic blood pressure; Per: Perindopril; SD: Standard deviation

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

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 \geq 95 and \leq 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/m². 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 10- Summary of Patient Demographics and Trial Design for PATH Study

Study #	Trial design	Dosage, route of administration and duration	Number of study subjects (randomized)	Age (years) Mean ± SD	Gender (%) 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 results

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 erbumine 16 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 erbumine 16 mg (26%, $p < 0.001$).

See results summarized in [Tables 11, 12](#).

Table 11 - 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 12- 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

DETAILED PHARMACOLOGY

Mechanism of action

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 ($IC_{50} = 2 \times 10^{-9}M$ and $800 \times 10^{-9}M$ 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 ($\geq 90\%$) 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.

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.

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 B₆C₃F₁ 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 <i>Salmonella typhimurium</i> and tryptophan-requiring <i>Escherichia coli</i> (Ames test)		
<i>Salmonella typhimurium</i> (TA100, TA1535, TA1537 and TA98) and <i>Escherichia coli</i> (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 the treatment)	Number of animal	Route of administration	Concentration (mg perindopril free acid/kg)	Major investigations	Conclusion
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 Toxicity

Fertility Studies

Studies were performed by administering 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	<p>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.</p> <p>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.</p> <p>Reduction in the number of ovules produced in the three groups. The mean number of corporea lutea ranged between 9.4 (-15% relative to the control group) and 10.0 (-9.9%).</p> <p>No abnormality related to the migration of the egg, its implantation or embryonic and fetal development was demonstrated.</p>
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	<p>Growth in the animals was retarded.</p> <p>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).</p> <p>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.</p> <p>The mortality of the G₁ pups was increased at the high dose (The mortality at birth was not altered 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 G₁ generation, the gestation of the G₁ females and the characteristics of the G₂ pups.</p>

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

Teratogenicity Studies

Studies were performed by administering 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

Toxicity Studies

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.

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PART III: CONSUMER INFORMATION

PrVIACORAM®

perindopril arginine and amlodipine tablets

This leaflet is part III of a three-part “Product Monograph” published when VIACORAM was approved for sale in Canada and is designed specifically for consumers. 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 VIACORAM®. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about VIACORAM®.

ABOUT THIS MEDICATION**What the medication is used for:**

VIACORAM® is used to treat mild to moderate high blood pressure. VIACORAM® should only be started in patients who are between the ages of 18 and 65.

What it does:

VIACORAM® is a combination of two active ingredients, perindopril arginine and amlodipine.

Perindopril arginine

- Is an angiotensin converting enzyme (ACE) inhibitor.
- ACE inhibitors help relax blood vessels and lower blood pressure by preventing ACE from producing angiotensin II which causes narrowing of blood vessels.

Amlodipine

- Is a calcium channel blocker.
- It blocks the transfer of calcium into the cells of the heart and blood vessels.
- This helps the blood vessels relax and to decrease blood pressure.

This medicine does not cure your disease. It is important to continue taking VIACORAM® regularly even if you feel fine. Do not stop taking your medicine without the advice of your doctor.

When it should not be used:

Do not take VIACORAM® if you:

- Are less than 18 years old.
- Are older than 65 and starting treatment.
- Are allergic (hypersensitive) to perindopril or any other ACE inhibitor, or to amlodipine or any other calcium antagonists, or to any non-medicinal ingredient in the formulation.
- Have experienced an allergic reaction (angioedema)

with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ACE inhibitor or without a known cause. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.

- Are taking a drug containing the combination of sacubitril/valsartan, due to the increased risk of serious allergic reaction which causes swelling of the face or throat (angioedema) when taken with VIACORAM®.
- Have kidney problems.
- Are already taking a blood pressure-lowering medicine that contains aliskiren and you have diabetes or kidney disease.
- Have been diagnosed with hereditary angioedema: an increased risk of getting an allergic reaction that is passed down through families. This can be triggered by different factors, such as surgery, flu, or dental procedures.
- Have narrowing of the mitral valve and left ventricular outflow tract obstruction (aortic stenosis, hypertrophic cardiomyopathy).
- Have heart failure.
- Are pregnant or intend 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®.
- Are on dialysis or any other type of blood filtration. Depending on the machine that is used, VIACORAM® may not be suitable for you.
- Have kidney problems where the blood supply to your kidneys is significantly reduced (renal artery stenosis).

What the medicinal ingredient is:

perindopril arginine and amlodipine.

What the non-medicinal ingredients are:

Microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal anhydrous silica.

What dosage forms it comes in:

VIACORAM® tablets are available in 3 combinations of perindopril/ amlodipine: 3.5 mg/2.5, 7 mg/5 mg, 14 mg/10 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions - Pregnancy
VIACORAM® should not be used during pregnancy. If you discover that you are pregnant while taking VIACORAM®, stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.

BEFORE you use VIACORAM® talk to your doctor, nurse or pharmacist if you:

- Are allergic to any drug used to lower blood pressure.
- Have hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery which supplies the kidney with blood).
- Have heart failure.
- Have a severe increase in blood pressure (hypertensive crisis).
- Are taking a medicine that contains aliskiren used to lower high blood pressure. The combination with VIACORAM® is not recommended.
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN".
- Have diabetes, heart, liver or kidney disease (including kidney transplantation).
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Are on a low-salt diet.
- Are less than 18 years old or are older than 65.
- Have systemic lupus erythematosus (SLE).
- 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.

Monitoring: Your physician may monitor your blood and kidney function while taking VIACORAM®.

Surgery: If you are going to have surgery and will be given an anesthetic, be sure to tell your doctor or dentist that you are taking VIACORAM®.

Driving and using machines: Wait until you know how you feel while taking VIACORAM® before driving or using machines. Dizziness, headache, fatigue, nausea, weariness or fainting can occur, especially after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or

alternative medicines.

The following may interact with VIACORAM®:

- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Allopurinol used to treat gout.
- Antidiabetic drugs, including insulin and oral medicines.
- Blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products, or angiotensin receptor blockers (ARBs).
- Lithium used to treat bipolar disorder.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include aspirin, ibuprofen, naproxen, and celecoxib.
- Vasodilators including nitrates (products that make the blood vessels become wider).
- Procainamide used to treat irregular heartbeats.
- Medicines to treat mental disorders such as depression, anxiety, schizophrenia etc (e.g. tricyclic antidepressants, antipsychotics, imipramine-like antidepressants, neuroleptics).
- Immunosuppressants (medicines which reduce the defence mechanism of the body) used for the treatment of auto-immune disorders or following transplant surgery (e.g. ciclosporin, tacrolimus).
- Heparin (medicines used to thin blood).
- Ephedrine, noradrenaline or adrenaline (medicines used to treat low blood pressure, shock or asthma).
- Baclofen used to treat muscle stiffness in diseases such as multiple sclerosis.
- Some antibiotics such as rifampicin, erythromycin, clarithromycin.
- Antiepileptic agents such as carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone,
- Itraconazole, ketoconazole (medicines used for treatment of fungal infections).
- Alpha-blockers used for the treatment of enlarged prostate such as prazosin, alfuzosin, doxazosin, tamsulosin, terazosin).
- Corticosteroids (used to treat various conditions including severe asthma and rheumatoid arthritis).
- Gold salts, especially with intravenous administration (used to treat symptoms of rheumatoid arthritis).
- Ritonavir, indinavir, nelfinavir (used to treat HIV).
- Trimethoprim (for the treatment of infections).
- Estramustine (used in cancer therapy).
- Hypericum perforatum (St John's wort, an herbal medicine used to treat depression).
- Simvastatin (a cholesterol lowering medicine).
- Anaesthetics.
- Treatment for bee and wasp allergies.
- Tetracosactide (used as a diagnostic agent in the clinic).
- Neutral endopeptidase (NEP) inhibitors. The

- combination with VIACORAM® is not recommended.
- Sirolimus, everolimus, temsirolimus and other drugs belonging to the class of mTOR inhibitors (used to avoid rejection of transplanted organs).

Grapefruit juice and grapefruit should not be consumed by people who are taking VIACORAM®. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of VIACORAM®.

PROPER USE OF THIS MEDICATION

Take VIACORAM® exactly as prescribed.

Tablets should be swallowed whole with a glass of water preferably at the same time each day, **in the morning**. It is recommended to take your dose before a meal.

Usual Adult dose:

The initial recommended dose is one tablet of VIACORAM® 3.5 mg/2.5 mg once daily.

After a month of treatment, depending on how you respond to the treatment, your doctor may increase the dose to 7mg/5mg once a day.

If your blood pressure is not controlled after 1 month of treatment with 7 mg/5 mg dose, your doctor may prescribe the 14 mg/10 mg VIACORAM® tablet once daily.

One tablet of VIACORAM® 14 mg/10 mg once a day is the maximum recommended dose for high blood pressure.

Overdose:

If you think you have taken too much VIACORAM® contact your doctor, nurse, pharmacist, 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, VIACORAM® can cause side effects, although not everybody gets them.

Side effects may include:

- cough,
- swelling in the tissues of the body (oedema),
- headache,

- diarrhea,
- nausea,
- dizziness,
- tiredness,
- itching (erythema).

If any of these affects you severely, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	Low Blood Pressure: dizziness, fainting, light-headedness. May occur when you go from lying or sitting to standing up.	√		
	Palpitations: unusual fast or irregular heartbeats			√
	Edema: swelling of the hands, ankles or feet	√		
	Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
Uncommon	Angina: sudden wheeziness, chest pain, shortness of breath, or difficulty in breathing			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect	Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help	
	Only if severe	In all cases		
Increased levels of potassium in the blood (hyperkalemia) : irregular heartbeat, muscle weakness and generally feeling unwell		√		
Angioedema and Severe Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√	
Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√		
Decreased Platelet: bruising, bleeding, fatigue and weakness		√		
Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect	Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help	
	Only if severe	In all cases		
	Cerebrovascular accident/Stroke : slurring speech, blurred vision, face drooping			√
Rare	Psoriasis aggravation		√	
Very rare	Inflammation of the pancreas (pancreatitis): abdominal pain that lasts and gets worse when you lie down, nausea and vomiting			√
	Severe skin reactions (Steven-Johnson Syndrome): intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes.			√
	Liver problems: abdominal pain, nausea, vomiting, loss of appetite, jaundice (yellowing of eyes and skin).		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	Myocardial infarction: heart attack, chest pain			√
Unknown	Extrapyramidal disorder: Muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want.		√	
	Phemphigoid: formation of blister clusters over the skin			√

This is not a complete list of side effects. For any unexpected effects while taking VIACORAM®, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

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.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available in the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at www.servier.ca or by contacting the sponsor, Servier Canada Inc., at: 1-800-363-6093

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