

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Coartil 8 mg/5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg perindopril tert-butylamine and 5 mg amlodipine (equivalent to 13.87 mg amlodipine besilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Coartil 8 mg + 10 mg tablets: this medicinal product is presented as white to off-white, round, biconvex tablets, engraved "5" on one side, with a diameter 9.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Coartil is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

4.2 Posology and method of administration

Posology

The fixed dose combination is not suitable for initial therapy. If the change of the dosage is needed, it should be carried out by individual titration of the free combination's ingredients.

Patients with renal impairment and elderly (see sections 4.4 and 5.2)

Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.

Coartil can be administered in patients with $Cl_{cr} \geq 60$ ml/min, and is not suitable for patients with $Cl_{cr} < 60$ ml/min. In these patients, an individual dose titration with the monocomponents is recommended.

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Patients with hepatic impairment: see sections 4.4 and 5.2

A dosage regimen for patients with hepatic impairment has not been established. Therefore, Coartil should be administered with caution.

Paediatric population

Coartil should not be used in children and adolescents as the efficacy and tolerability of perindopril alone or in combination with amlodipine, have not been established in children and adolescents.

Method of administration

Oral route.

One tablet per day as a single dose, preferably to be taken in the morning and before a meal.

4.3 Contraindications

Linked to perindopril

- Hypersensitivity to perindopril or to any other ACE inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

Linked to amlodipine

- Severe hypotension,
- Hypersensitivity to amlodipine or to any other dihydropyridines,
- Shock, including cardiogenic shock,
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis),
- Haemodynamically unstable heart failure after acute myocardial infarction.

Linked to Coartil

All contraindications related to each monocomponent, as listed above, should apply also to the fixed combination of Coartil.

- Hypersensitivity to any of the excipients listed in section 6.1.
- The concomitant use of Coartil with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1)."

4.4 Special warnings and precautions for use

All warnings related to each monocomponent, as listed below, should also apply also to the fixed combination of Coartil .

Linked to
perindopril
Special warnings

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, Coartil 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, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

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

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8).

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

Anaphylactoid reactions during 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.

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. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril 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).

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Precautions for use

Hypotension:

ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients at high risk of symptomatic hypotension, blood pressure, renal function and serum potassium should be monitored closely during treatment with Coartil.

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.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy:

As with other ACE inhibitors, perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal impairment:

In cases of renal impairment (creatinine clearance < 60 ml/min) an individual dose titration with the monocomponents is recommended (see section 4.2).

Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8).

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

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see section 4.8).

Ethnic differences:

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough:

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

Surgery/Anaesthesia:

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Coartil may block angiotensin II formation secondary to compensatory renin release. The treatment 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.

Hyperkalaemia:

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia 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), potassium supplements or potassium containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, cotrimoxazole also known as trimethoprim/sulfamethoxazole). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of perindopril and any of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Diabetic patients:

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

*Linked to
amlodipine:
Precautions for
use*

Patients with impaired hepatic function:

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established.

Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Patients with heart failure:

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase

the risk of future cardiovascular events and mortality.

Patients with renal impairment:

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

Elderly patients

In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

Linked to Coartil

Precautions for use

Interactions

The concomitant use of Coartil with lithium, potassium-sparing diuretics or potassium supplements is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Linked to perindopril

Concomitant use not recommended:

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone- system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes: Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. Potassium- sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements or potassium containing salt substitutes may lead to significant increases in serum potassium. Therefore, the combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium:

Reversible increases in serum lithium concentrations and toxicity (severe neurotoxicity) have been reported during concurrent use of ACE inhibitors. The combination of perindopril with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended (see section 4.4).

Estramustine:

Risk of increased adverse effects such as angioneurotic oedema (angioedema).

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

Concomitant use which requires special care:

Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid ≥ 3 g/day:

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

Antidiabetic agents (insulin, hypoglycaemic sulphonamides):

The use of angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides. The onset of hypoglycaemic episodes is very rare (there is probably an improvement in glucose tolerance with a resulting reduction in insulin requirements).

Concomitant use to be taken into consideration: Diuretics:

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Gold:

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

Racecadotril:

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

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

Linked to amlodipine

Concomitant use which requires special care:

CYP3A4 inhibitors:

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

CYP3A4 inducers (rifampicin, Hypericum perforatum, anticonvulsant agents i.e carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone):

The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine due to an increase of the hepatic

metabolism of amlodipine by these inducers. Amlodipine should be used with caution together with CYP3A4 inducers and posology of amlodipine could be adapted if needed.

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

Dantrolene (infusion)

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

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure- lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus:

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Clarithromycin:

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co administered with clarithromycin.

Cyclosporine:

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

Simvastatin:

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 in patients on amlodipine to 20 mg daily.

Concomitant use to be taken into consideration:

Beta-blockers used in heart failure (bisoprolol, carvedilol, metoprolol): Risk of hypotension, heart weakness in patients with cardiac heart

failure, be it latent or uncontrolled (addition of negative inotropic effect). Furthermore, the beta-blocker may minimize the sympathetic reflex in case of excessive haemodynamic repercussion.

Others combinations:

In monotherapy, amlodipine has been safely administered with thiazide diuretics, ACE inhibitors, long-acting nitrates, sublingual nitroglycerine, digoxin, warfarin,

atorvastatin, sildenafil, anti-acid medicines (aluminium hydroxide gel, magnesium hydroxide, simeticone), cimetidine, non-steroidal antiinflammatory medicines, antibiotics and oral hypoglycaemic medicines.

Indeed, specific studies conducted with some drugs have shown no influence on amlodipine:

- when sildenafil and amlodipine were used in combination, each one independently exerted its own blood pressure lowering effect.

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

Concomitant use which requires special care:

Baclofen. Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adjustment of the antihypertensive if necessary.

Concomitant use to be taken into consideration:

- Antihypertensive agents (such as beta-blockers) and vasodilators:
- Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine.
- Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.
- Corticosteroids, tetracosactide: reduction in antihypertensive effect (salt and water retention due to corticosteroids).
- Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin): increased antihypertensive effect and increased risk of orthostatic hypotension.
- Amifostine: may potentiate the antihypertensive effect of amlodipine.
- Tricyclic antidepressants/antipsychotics/anaesthetics: increased antihypertensive effect and increased risk of orthostatic hypotension.

4.6 Fertility, pregnancy and lactation

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

Coartil is not recommended during the first trimester of pregnancy.

Coartil is contraindicated during the second and third

trimesters of pregnancy.

Coartil is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Coartil taking into account the importance of this therapy for the mother.

Pregnancy

Linked to perindopril

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE

inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.) Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Linked to amlodipine

The safety of amlodipine in human pregnancy has not been established. Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery. In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.

Breast feeding

Linked to perindopril

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

Linked to amlodipine

It is not known whether amlodipine is excreted in breast milk. Similar calcium channel blockers of the dihydropyridine type are excreted in breast milk.

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

Fertility

Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of Coartil on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with perindopril or amlodipine given separately and ranked under the MedDRA classification by body system and under the following frequency:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	Perindopril
Blood and lymphatic system disorders	Leucopenia/neutropenia (see section 4.4)	Very rare	Very rare
	Agranulocytosis or pancytopenia (see section 4.4)		Very rare
	Thrombocytopenia (see section 4.4)	Very rare	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)	-	Very rare
	Decrease in haemoglobin and haematocrit	-	Very rare
Immune system disorders	Allergic reaction: Urticaria	Very rare	Uncommon
Metabolism and	Hyperglycaemia	Very rare	-

nutrition disorders	Hypoglycaemia (see sections 4.4 and 4.5)	-	Not known
Psychiatric disorders	Insomnia	Uncommon	-
	Mood changes	Uncommon	Uncommon
	Depression	Uncommon	-
	Sleep disturbances	-	Uncommon
Nervous system disorders	Somnolence	Common	-
	Dizziness	Common	Common
	Headache (especially at the beginning of the treatment)	Common	Common
	Tremor	Uncommon	-
	Hypoesthesia, Paresthesia	Uncommon	-
		Uncommon	Common
	Hypertonia	Very rare	-
	Peripheral neuropathy	Very rare	-
	Vertigo	-	Common
	Confusion	Rare	Very rare
	Extrapyramidal disorder	Not known	-
Eye disorders	Visual disturbances (including diplopia)	Common	Common
Ear and labyrinth disorders	Tinnitus	Uncommon	Common
Cardiac disorders	Palpitations	Common	-
	Syncope	Uncommon	-
	Angina pain	Rare	-
	Angina pectoris	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see	Very rare	Very rare

	section 4.4)		
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Uncommon	Very rare
Vascular disorders	Flushing	Common	-
	Hypotension (and effects related to hypotension)	Uncommon	Common
	Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
	Vasculitis	Very rare	Not known
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common	Common
	Rhinitis	Uncommon	Very rare
	Cough	Uncommon	Common
	Bronchospasm	-	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastrointestinal disorders	Gingival hyperplasia	Very rare	-
	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)	Common	Common
	Vomiting	Uncommon	Common
	Dry mouth	Uncommon	Uncommon
	Dysgeusia	Uncommon	Common
	Pancreatitis	Very rare	Very rare
	Gastritis	Very rare	-
Hepatobiliary disorders	Hepatitis, cholestatic jaundice	Very rare	-
	Hepatitis either cytolytic or cholestatic (see section 4.4)	-	Very rare
Skin and subcutaneous tissue disorders	Quincke's oedema	Very rare	-
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)	-	Uncommon
	Erythema multiform	Very rare	Very rare
	Alopecia	Uncommon	-
	Purpura	Uncommon	-
	Skin discoloration	Uncommon	-
	Increased sweating	Uncommon	Uncommon
	Exfoliative dermatitis	Very rare	-
	Pruritus	Uncommon	Common
	Exanthema, urticaria	Uncommon	-
	Photosensitivity	Very rare	-
	Rash	Uncommon	Common
	Stevens-Johnson Syndrome	Very rare	-
	Psoriasis aggravation	-	Rare
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	-
	Myalgia	Uncommon	Uncommon
	Muscle cramps, ankle swelling	Common	Common
	Back pain	Uncommon	-
Renal and urinary disorders	Micturition disorder, nocturia, increased urinary frequency	Uncommon	-
	Renal impairment	-	Uncommon
	Acute renal failure	-	Very rare
Reproductive system and breast disorders	Impotence	Uncommon	Uncommon
	Gynaecomastia	Uncommon	

General disorders and administration site conditions	Oedema, peripheral oedema	Very common	-
	Fatigue	Common	-
	Chest pain	Uncommon	-
	Asthenia	Common	Common
	Pain	Uncommon	-
	Malaise	Uncommon	-
Investigations	Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis)	Very rare	-
	Serum bilirubin and liver enzymes elevation	-	Rare
	Increases in blood urea and serum creatinine, hyperkalaemia (see section 4.4)	-	Not known
	Weight gain	Uncommon	-
	Weight decrease	Uncommon	-

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board PVERS portal: <https://pv.pharmacyboardkenya.org>".

4.9 Overdose

There is no information on overdose with Coartil in humans.

For amlodipine, experience with intentional overdose in humans is limited. Large overdosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Any hypotension due to amlodipine overdosage calls for a monitoring in cardiologic intensive care unit. 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.

Amlodipine is not dialyzable.

For perindopril, limited data are available for overdose in humans. Symptoms associated with the overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril can be removed from the

systemic circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for treatment-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors and calcium channel blockers, ATC code: C09BB04.

Perindopril

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide.

Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity *in vitro*.

Hypertension:

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.

The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100% of peak effects.

The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a

rebound effect. Perindopril reduces left ventricular hypertrophy.

In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries.

Patients with stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) (n=6110) or placebo (n=6108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers. The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] - p<0.001).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] - p<0.001) in the primary endpoint was observed by comparison to placebo.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should

therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Amlodipine

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully understood but is determined by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilation increases the supply in oxygen to myocardium in patients with Prinzmetal's angina attack.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) throughout the 24 hour interval.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression. Amlodipine decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug (amlodipine or ACE-inhibitor as first-line) therapies to that of the thiazide diuretic, in mild to moderate hypertension. There were no significant difference in cardiovascular outcomes between amlodipine-based therapy and thiazide diuretic-based therapy.

Paediatric population

In a study involving 268 children aged 6-17 years with predominantly

secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2 Pharmacokinetic properties

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

Perindopril

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

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

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

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

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentrationdependent. Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure (see section 4.2). Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

Amlodipine

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. Its bioavailability is not influenced by food. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

Amlodipine is extensively metabolised by the liver to inactive metabolites. About 60% of the administered dose is excreted in the urine, 10% as unchanged amlodipine.

Use in the elderly: the time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. The recommended dosage regimen for the elderly is the same, although increasing the dose should take place with caution.

Use in patients with renal failure: see section 4.2

Use in patients with impaired hepatic function: As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function.

Paediatric population

A population PK study has been conducted in 74 hypertensive children aged from

12 months to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/h respectively in males and 16.4 and 21.3 L/h respectively in females. Large variability in exposure between individuals was observed. Data reported in

children below 6 years is limited.

5.3 **Preclinical safety data**

Perindopril

In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

No mutagenicity has been observed in *in vitro* or *in vivo* studies.

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

No carcinogenicity has been observed in long term studies in rats and mice.

Amlodipine

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

Reproductive studies have shown that calcium antagonists induce embryotoxic and/or teratogenic effects in several species, mainly as distal skeletal malformations.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle- stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose type 112
microcrystalline cellulose type 200
sodium starch glycolate
colloidal anhydrous silica
magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30months

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Blister (OPA/Alu/PVC-Alu): 14, 20, 28, 30, 56, 60, 90 in a carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation Holder

Pharma Bavaria Internacional (PBI) Portugal, Unipessoal Lda.
Viela da Beloura, n°6, Lj 19

2710- 693 Sintra
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Manufacturer

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Poland

8 MARKETING AUTHORISATION NUMBER(S)

CTD10540

9 DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

16/12/2025

10 DATE OF REVISION OF THE TEXT

16/12/2025