

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

COVERAM 5 mg/5 mg tablets

COVERAM 5 mg/10 mg tablets

COVERAM 10 mg/5 mg tablets

COVERAM 10 mg/10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 3.395 mg perindopril equivalent to 5 mg perindopril arginine and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.

[One tablet contains 3.395 mg perindopril equivalent to 5 mg perindopril arginine and 13.870 mg amlodipine besilate equivalent to 10 mg amlodipine]

[One tablet contains 6.790 mg perindopril equivalent to 10 mg perindopril arginine and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine]



[One tablet contains 6.790 mg perindopril equivalent to 10 mg perindopril arginine and 13.870 mg amlodipine besilate equivalent to 10 mg amlodipine]



Excipient with known effect: lactose monohydrate.



For the full list of excipients, see section 6.1.



3. PHARMACEUTICAL FORM

Tablet.

White, rod-shaped tablet, 8.5 mm long and 4.5 mm wide, engraved with 5/5 on one face and   on the other face.

[White, square-shaped tablet, 8 mm long and 8 mm wide, engraved with 5/10 on one face and   on the other face.]

[White, triangular-shaped tablet, 9.5 mm x 8.8 mm x 8.8 mm, engraved with 10/5 on one face and   on the other face.]

[White, round tablet, 8.5 mm diameter, engraved with 10/10 on one face and   on the other face.]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Coveram 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

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

The fixed dose combination is not suitable for initial therapy.

If a change of posology is required, the dose of Coveram could be modified or individual titration with free combination may be considered.

Method of administration

For oral use.

Special populations

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

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

Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Patients with hepatic impairment: see sections 4.4 and 5.2

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lowest effective dose (see sections 4.4 and 5.2). To find the optimal starting dose and maintenance dose of patients with hepatic impairment, the patients should be individually titrated using the free combination of amlodipine and perindopril. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Paediatric population

Coveram should not be used in children and adolescents as the efficacy and safety of perindopril and amlodipine, in combination, have not been established.

4.3 Contraindications

Linked to perindopril:

- Hypersensitivity to the active substance or to any other angiotensin converting enzyme (ACE) inhibitor,
- History of angioedema associated with previous ACE inhibitor therapy (see section 4.4),
- Hereditary or idiopathic angioedema,
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6),
- Concomitant use of Coveram with aliskiren-containing products in patients with diabetes mellitus or renal impairment ($\text{GFR} < 60\text{ ml/min/1.73 m}^2$) (see sections 4.5 and 5.1),
- Concomitant use with sacubitril/valsartan therapy. Perindopril-containing treatment must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5),
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5),
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4).

Linked to amlodipine:

- Severe hypotension,
- Hypersensitivity to the active substance or to dihydropyridines derivatives,
- 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 Coveram:

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

- Hypersensitivity to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

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

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE inhibitor.

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

Patients receiving ACE inhibitors during (LDL) apheresis with dextran sulphate adsorption have experienced anaphylactoid reactions, which could be fatal. 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 these patients, these reactions have been avoided when the ACE inhibitor were temporarily withheld, but they however 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 risk 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 risk factors, especially if there is pre-existing impaired renal function. Some of these patients developed severe 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).

Renovascular hypertension:

There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors (see section 4.3). 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.

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 impairment of renal function (including risk of 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).

However, if dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, blood electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Primary hyperaldosteronism:

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

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitors is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have a well 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).

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 Coveram.

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).

Periodic monitoring of potassium and creatinine are part of normal medical practice for these patients (see section 4.8).

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

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and may progress 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 specificities:

A higher rate of angioedema has been observed in black patients treated with ACE inhibitors.

As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people considering the higher prevalence of low-renin states in in this type of 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, Coveram may block angiotensin II formation secondary to 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, ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Risk factors for the development of hyperkalaemia include renal insufficiency, alteration of renal function, age (> 70 years), diabetes mellitus, intercurrent events, such as dehydration, acute cardiac decompensation, metabolic acidosis, or concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements; potassium-containing salt substitutes; other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists or angiotensin-receptor blockers. The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias.

Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored. If concomitant use of perindopril and any of the above mentioned agents is deemed necessary, 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, particularly during the first month of treatment with an ACE inhibitor (see section 4.5).

Linked to amlodipine:

Precautions for use

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

Cardiac 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 (see section 5.1). Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of cardiovascular events and mortality.

Hepatic impairment:

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 lowest effective dose 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.

Elderly:

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

Renal failure:

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.

Linked to Coveram

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

Precautions for use

Excipients:

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

Interactions:

The concomitant use of Coveram with lithium, potassium-sparing drugs or potassium supplements, or dantrolene is not recommended (see section 4.5)

4.5 Interaction with other medicinal products and other forms of interaction

Linked to perindopril

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).

Drugs increasing the risk of angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4). Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk for angioedema (see section 4.4).

Drugs inducing hyperkalaemia:

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with Coveram. Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia, such as aliskiren, potassium salts, potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. The combination of these drugs increases the risk of hyperkalaemia. Therefore, the combination of Coveram with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Concomitant use contra-indicated (see section 4.3):

Aliskiren:

In diabetic or impaired renal patients, risk of hyperkalaemia, alteration of renal function and cardiovascular morbidity and mortality increase.

Extracorporeal treatments:

Extracorporeal treatments leading to contact with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate are contraindicated due to an increased risk of anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Concomitant use not recommended (see section 4.4):

Aliskiren:

In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, alteration of renal function and cardiovascular morbidity and mortality increase.

Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker:

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with ACE inhibitor and angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and alteration of renal function (including acute renal failure) as compared to use of a single RAAS agent. Dual blockade (e.g. by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure.

Estramustine:

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

Potassium-sparing diuretics (e.g. triamterene, amiloride; etc.), potassium salts:

Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects).

The combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is nonetheless indicated, they should be used with caution and with periodic monitoring of serum potassium. For use of spironolactone in heart failure, see below.

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).

Concomitant use which requires special care:

Antidiabetic agents (insulins, oral hypoglycaemic agents):

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may increase the blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon seems to occur in patients with renal impairment during the first weeks of combined treatment.

Non-potassium-sparing diuretics:

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience high reduction in blood pressure after initiation of therapy with an ACE inhibitor. The hypotensive effect 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.

In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE inhibitor must be initiated with a low dose and progressively increased.

In diuretic-treated congestive heart failure, the ACE inhibitor should be initiated at a very low dose, after reducing the dose of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE inhibitor therapy.

Potassium-sparing diuretics (eplerenone, spironolactone):

With eplerenone or spironolactone at doses between 12.5 mg to 50 mg by day and with low doses of ACE inhibitors:

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

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

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

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

When ACE-inhibitors are administered simultaneously with NSAIDs (such as acetylsalicylic acid at anti-inflammatory dose 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 a risk of acute renal failure, and an increase in serum potassium, especially in patients with impaired 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 at the start of the treatment and periodically thereafter.

Concomitant use to be taken into account:

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Gold salts:

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.

Linked to amlodipine

Concomitant use not recommended:

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.

Concomitant use which requires special care:

CYP3A4 inducers: Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose adjustment considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, St John's wort [*hypericum perforatum*]).

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

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

Concomitant use to be taken into account:

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. In order to avoid toxicity of tacrolimus, administration of amlodipine in patients treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Being a weak CYP3A inhibitor, amlodipine may increase exposure of mTOR inhibitor when used concomitantly.

Ciclosporine:

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

Simvastatin:

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin results 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.

Others combinations:

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

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.

Linked to Coveram:

Concomitant use which requires special care:

Baclofen:

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

Concomitant use to be taken into account :

- . Antihypertensive agents (such as beta-blockers) and vasodilators:
Concomitant use of these antihypertensive 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 should therefore 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/anaesthetic: 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:

Coveram is not recommended during the first trimester of pregnancy. Coveram is contraindicated during the second and third trimesters of pregnancy.

Coveram is not recommended during lactation. A decision should therefore be made whether to discontinue breast-feeding or to discontinue the treatment taking account the importance of this therapy for the mother.

Pregnancy:

Linked to perindopril

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimesters 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 of congenital malformations cannot be excluded. Unless ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have a well 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 foetotoxicity (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 have their blood pressure closely observed (see also sections 4.3 and 4.4).

Linked to amlodipine

The safety of amlodipine in human pregnancy has not been established.

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 foetus.

Breast-feeding:

Linked to perindopril

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

Linked to amlodipine

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated at an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.. A decision on whether to continue/discontinue 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:

Linked to perindopril

There was no effect on reproductive performance or fertility.

Linked to amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of Coveram on the ability to drive and use machines have been performed. Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients treated with amlodipine suffer from dizziness, headache, fatigue, weariness or nausea, their ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

a. Summary of safety profile

The most commonly reported adverse reactions with perindopril and amlodipine given separately are: oedema, somnolence, dizziness, headache (especially at the beginning of the treatment), dysgeusia, paraesthesia, visual impairment (including diplopia), tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), dyspnoea, cough, abdominal pain, nausea, vomiting, dyspepsia, change of bowel habit, diarrhoea, constipation, prurit, rash, exanthema, joint swelling (ankle swelling), muscle spasms, fatigue, asthenia.

b. Tabulated list of adverse reactions:

The following undesirable effects have been observed during clinical trials and/or post-marketing use 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).

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	Perindopril
Infections and infestations	Rhinitis	Uncommon	Very rare
Blood and the lymphatic System Disorders	Eosinophilia	-	Uncommon*
	Leukopenia/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 enzyme specific in patients with a congenital deficiency of G6PDH (see section 4.4)	-	Very rare
Immune System Disorders	Hypersensitivity	Very rare	Uncommon
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	-	Rare
Metabolism and Nutrition Disorders	Hypoglycaemia (see sections 4.4 and 4.5)	-	Uncommon*
	Hyperkalaemia, reversible on discontinuation (see section 4.4)	-	Uncommon*
	Hyponatraemia	-	Uncommon*
	Hyperglycaemia	Very rare	-
Psychiatric disorders	Insomnia	Uncommon	-
	Mood altered (including anxiety)	Uncommon	Uncommon
	Depression	Uncommon	Uncommon*
	Sleep disorder	-	Uncommon
Nervous System disorders	Somnolence (especially at the beginning of the treatment)	Common	Uncommon*
	Dizziness (especially at the beginning of the treatment)	Common	Common
	Headache (especially at the beginning of the treatment)	Common	Common
	Dysgeusia	Uncommon	Common
	Tremor	Uncommon	-
	Hypoaesthesia	Uncommon	-
	Paraesthesia	Uncommon	Common
	Syncope	Uncommon	Uncommon*
	Confusional state	Rare	Very rare
Hypertonia	Very rare	-	

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	Perindopril
	Neuropathy peripheral	Very rare	-
	Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
	Extrapyramidal disorder (extrapyramidal syndrome)	Not known	-
Eye Disorders	Visual impairment	Common	Common
	Diplopia	Common	-
Ear and labyrinth disorders	Tinnitus	Uncommon	Common
	Vertigo	-	Common
Cardiac Disorders	Palpitations	Common	Uncommon*
	Tachycardia	-	Uncommon*
	Angina pectoris (see section 4.4)	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	Very rare	Very rare
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Uncommon	Very rare
Vascular Disorders	Flushing	Common	Rare*
	Hypotension (and effects related to hypotension)	Uncommon	Common
	Vasculitis	Very Rare	Uncommon*
	Raynaud's phenomenon	-	Not known

Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Common	Common
	Cough	Uncommon	Common
	Bronchospasm	-	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastro-intestinal Disorders	Gingival hyperplasia	Very rare	-
	Abdominal pain	Common	Common
	Nausea	Common	Common
	Vomiting	Uncommon	Common
	Dyspepsia	Common	Common
	Change of bowel habit	Common	-
	Dry mouth	Uncommon	Uncommon
	Diarrhoea	Common	Common
	Constipation	Common	Common
	Pancreatitis	Very rare	Very rare
	Gastritis	Very rare	-
Hepato-biliary Disorders	Hepatitis, jaundice	Very rare	-
	Hepatitis either cytolytic or cholestatic (see section 4.4)	-	Very rare
	Hepatic enzymes increased (mostly consistent with cholestasis)	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)	Very rare	Uncommon
	Erythema multiform	Very rare	Very rare
	Alopecia	Uncommon	-
	Purpura	Uncommon	-
	Skin discolouration	Uncommon	Uncommon
	Hyperhidrosis	Uncommon	Uncommon
	Pruritus	Uncommon	Common
	Rash, exanthema	Uncommon	Common
	Urticaria (see section 4.4)	Uncommon	Uncommon
	Photosensitivity reactions	Very rare	Uncommon*
	Pemphigoid	-	Uncommon*
	Psoriasis aggravation	-	Rare
	Stevens-Johnson Syndrome	Very rare	-
	Exfoliative dermatitis	Very rare	-
Toxic epidermal necrolysis	Not known	-	
	Joint swelling (ankle swelling)	Common	-
	Arthralgia	Uncommon	Uncommon*

Musculoskeletal and Connective Tissue Disorders	Myalgia	Uncommon	Uncommon*
	Muscle spasms	Common	Common
	Back pain	Uncommon	-
Renal and Urinary Disorders	Micturition disorder, nocturia, pollakiuria	Uncommon	-
	Renal failure	-	Uncommon
	Acute renal failure	-	Rare
	Anuria/Oliguria	-	Rare*
Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon	Uncommon
	Gynaecomastia	Uncommon	-
General Disorders and Administration Site Conditions	Oedema	Very common	-
	Oedema peripheral	-	Uncommon*
	Fatigue	Common	-
	Chest pain	Uncommon	Uncommon*
	Asthenia	Common	Common
	Pain	Uncommon	-
	Malaise	Uncommon	Uncommon*
	Pyrexia	-	Uncommon*
Investigations	Weight increased, weight decreased	Uncommon	-
	Blood urea increased	-	Uncommon*
	Blood creatinine increased	-	Uncommon*
	Blood bilirubin increase	-	Rare
	Hepatic enzyme increase	-	Rare
	Haemoglobin decreased and haematocrit decreased	-	Very rare
Injury, poisoning and procedural complications	Fall	-	Uncommon*

* Frequency estimated from clinical trial data for the undesirable effects reported post-marketing as spontaneous notifications

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 via the national reporting system.

4.9 Overdose

There is no information on overdose with Coveram in humans.

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

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

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment: clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of lower extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

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

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

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

The recommended treatment of overdose is intravenous infusion of normal sodium chloride solution. If hypotension occurs, the patient should be placed in supine position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for treatment-resistant bradycardia. Vital signs, serum electrolytes and creatinine levels should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and calcium channel blockers, ATC code: C09BB04.

Perindopril:

Mechanism of action

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*.

Clinical efficacy and safety

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 elasticity of the main arterial trunks and decreases the media:lumen ratio of small arteries.

Stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

A total of 12,218 patients aged over 18 were randomised to 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) (n=6,110) or placebo (n=6,108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had 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.

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

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 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 and 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 renal failure 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 renal failure, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (such as hyperkalaemia, hypotension and renal failure) were more frequently reported in the aliskiren group than in the placebo group.

Amlodipine:

Mechanism of action

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

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

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

Clinical efficacy and safety

In patients with hypertension, once daily administration of amlodipine provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due its progressive action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and 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 thus suitable for use in patients with asthma, diabetes, and gout.

Coronary artery disease (CAD):

The efficacy of amlodipine in preventing clinical events in patients with (CAD) has been evaluated in an independent, multi-centre, randomized, double- blind, placebo-controlled study of 1,997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Table 1. Incidence of significant clinical outcomes for CAMELOT					
Outcomes	Cardiovascular event rates, No. (%)			Amlodipine vs. placebo	
	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	P Value
<u>Primary Endpoint</u>					
Adverse cardiovascular events	<u>110 (16.6)</u>	<u>151 (23.1)</u>	<u>136 (20.2)</u>	<u>0.69 (0.54-0.88)</u>	<u>.003</u>

<u>Individual Components</u>					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	.002
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24

Abbreviations: CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack, CHF, congestive heart failure.

Heart failure:

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT):

A randomized double-blind morbidity and mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke > 6 months or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 (95% CI(0.90-1.07) p=0.65). Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs 7.7%, RR 1.38, (95% CI [1.25-1.52] p<0.001)). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy, RR 0.96 (95% CI [0.89-1.02] p=0.20).

5.2 Pharmacokinetic properties

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

Perindopril:

Absorption

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

Perindopril is a prodrug. The bioavailability of perindoprilat the active metabolite is 27%. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

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

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

Distribution

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Binding of perindoprilat to plasma proteins is 20%, principally to ACE, and is concentration-dependent.

Elimination

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

Elderly, heart Failure, renal Failure

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.

Hepatic impairment

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:

Absorption, distribution, plasma protein binding

After oral administration of therapeutic doses, amlodipine is fully 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. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/Elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

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. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Hepatic impairment

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

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, ACE inhibitors, as a class, have been shown to induce adverse effects on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed. Fertility was not impaired either in male or in female rats.

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

Amlodipine:

Reproductive toxicology

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 dose for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 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.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dose 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.

* Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470B)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the container tightly closed in order to protect from moisture. Store in the original package. Store below 30 °C.

6.5 Nature and contents of container

10 or 30 tablets in polypropylene container equipped with a low density polyethylene flow reducer and a low density polyethylene stopper containing a desiccant gel.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER - FRANCE

8. MARKETING AUTHORISATION NUMBER

See country marketing authorisation

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

See country marketing authorisation

10. DATE OF REVISION OF THE TEXT

16.08.2022

11. DOSIMETRY

NA

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

NA

PRESCRIPTION AND DISPENSING CONDITIONS

LIST I