

COVERAM® 5 mg / 5 mg tablets
perindopril arginine / amlodipine

COVERAM® 5 mg / 10 mg tablets
perindopril arginine / amlodipine

COVERAM® 10 mg / 5 mg tablets
perindopril arginine / amlodipine

COVERAM® 10 mg / 10 mg tablets
perindopril arginine / amlodipine

COMPOSITION

COVERAM 5mg / 5mg

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

COVERAM 5mg / 10mg

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

COVERAM 10mg / 5mg

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


COVERAM 10mg / 10mg

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


PHARMACEUTICAL FORM

Tablet.

COVERAM 5mg / 5mg

White, rod-shaped tablet engraved with 5/5 on one face and  on the other face.

COVERAM 5mg / 10mg

White, square-shaped tablet engraved with 5/10 on one face and  on the other face.

COVERAM 10mg / 5mg

White, triangular-shaped tablet engraved with 10/5 on one face and  on the other face.

COVERAM 10mg / 10mg

White, round tablet engraved with 10/10 on one face and  on the other face.

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.

POSOLGY AND METHOD OF ADMINISTRATION

Posology

Oral route.

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.

Special populations

Patients with renal impairment and older people (see section "Special warnings and precautions for use" and "Pharmacokinetic properties")

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

Coveram can be administered in patients with Cl_{cr} ≥ 60ml/min, and is not suitable for patients with Cl_{cr} < 60ml/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 "Special warnings and precautions for use" and "Pharmacokinetic properties")

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 lower end of the dosing range (see sections "Special warnings and precautions for use" and "Pharmacokinetic properties"). 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 populations

Coveram should not be used in children and adolescents (less than 18 years) as the efficacy and tolerability of perindopril and amlodipine, alone or in combination, have not been established in children and adolescents.

CONTRAINDICATIONS

Linked to perindopril:

- Hypersensitivity to the active substance 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 "Special Warnings and precautions for use" and "Pregnancy and lactation").
- Concomitant use of COVERAM with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections "Interaction with other medicinal products and other forms of interaction" and "Pharmacodynamic properties").

- Concomitant use with sacubitril/valsartan (see sections "Special Warnings and precautions for use" and "Interaction with other medicinal products and other forms of interaction"),
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section "Interaction with other medicinal products and other forms of interaction"),
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section "Special warnings and precautions for use").

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),
- Unstable angina pectoris (excluding Prinzmetal's angina),
- Heart failure after acute myocardial infarction (during the first 28 days).

Linked to Coveram

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

- Hypersensitivity to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

All warnings related to each monocomponent, as listed below, should also apply 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 "Undesirable effects"). 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 an increased risk of angioedema while receiving an ACE inhibitor (see section "Contraindications").

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 "Undesirable effects").

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section "Contraindication"). 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 "Contraindication" and "Interaction with other medicinal products and other forms of interaction"). Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE inhibitors may also increase the risk of angioedema (see section "Interaction with other medicinal products and other forms of interaction"). Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

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 "Interaction with other medicinal products and other forms of interaction").

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).

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 "Contraindications"). Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

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 "Interaction with other medicinal products and other forms of interaction" and "Pharmacodynamic properties").

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

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

Primary aldosteronism:

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

Pregnancy

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 an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatments with ACE inhibitors should be stopped immediately and, if appropriate, alternative therapy should be started (see sections "Contraindications" and "Fertility, pregnancy and lactation").

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 "Interaction with other medicinal products and other forms of interaction" and "Undesirable effects"). 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 9mg/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 "Posology and method of administration").

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

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

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 "Undesirable effects").

Race

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 levels 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 anaesthesia with agents that produce hypotension, COVERAM 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.

Hyperkalemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of perindopril 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 "Interaction with other medicinal products and other forms of interaction").

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 "Interaction with other medicinal products and other forms of interaction").

Linked to amlodipine

Precautions for use

Hepatic failure:

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function. Amlodipine should therefore be administered with caution in these patients and with a close monitoring of the hepatic enzymes.

Heart failure:

Amlodipine should be administered with caution in patients with cardiac failure.

In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with grade III or IV heart failure of non-ischaemic aetiology (NYHA Classification, New York Heart Association Classification), amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section "Pharmacodynamic properties").

Linked to Coveram

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

Precautions for use

Excipients

Due to the presence of lactose, patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption, or total lactase deficiency 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 "Interaction with other medicinal products and other forms of interaction").

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 "Contraindication", "Special warnings and precautions for use" and "Pharmacodynamic properties").

Drugs inducing hyperkalaemia:

Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and fixed dose combination with sulfamethoxazole (Co-trimoxazole).

The combination of these drugs increases the risk of hyperkalaemia.

Concomitant use contra-indicated (see section

"Contraindication"):

Aliskiren:

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

Extracorporeal treatments:

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

Sacubitril/valsartan:

The concomitant use of perindopril with sacubitril/valsartan is contra-indicated as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after taking the last dose of sacubitril/valsartan (see section "Contraindication" and "Special warnings and precautions for use").

Concomitant use not recommended (see section “Special warnings and precautions for use”):

Aliskiren:

In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening 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 worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system 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 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 “Special warnings and precautions for use”).

Potassium-sparing diuretics (e.g. triamterene, amiloride...), 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 “Special warnings and precautions for use”). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see below.

Lithium:

Reversible increases in serum lithium concentrations and toxicity (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 “Special warnings and precautions for use”).

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 cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Non-potassium-sparing diuretics:

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

In diuretic-treated congestive heart failure, the ACE inhibitor should be initiated at a very low dosage, possibly after reducing the dosage 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 12.5mg to 50mg by day and with low doses of ACE inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction <40%, and previously treated with ACE inhibitors and loop diuretics, risk of 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 creatinemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

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 “Special warnings and precautions for use”).

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

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of 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.

Concomitant use which requires some care:

Gliptines (linagliptine, saxagliptine, sitagliptine, vildagliptine):

Increased risk of angio-oedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptine, in patients co-treated with an ACE inhibitor.

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.

Linked to amlodipine

Concomitant use not recommended

Dantrolene (infusion)

In animals, lethal ventricular fibrillations are observed after I.V. administration of verapamil and dantrolene. By extrapolation, the combination of amlodipine and dantrolene should be avoided.

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 regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

CYP3A4 inhibitors (itraconazole, ketoconazole)

Co-administration may increase the plasma concentration of amlodipine and consequently its adverse effects. Caution should be exercised when combining amlodipine with itraconazole or ketoconazole: the posology of amlodipine should be adjusted if needed.

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 inotrope effect). Furthermore, the beta-blocker may minimize the sympathetic reflex in case of excessive haemodynamic repercussion.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Others combinations

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicines (aluminium hydroxide gel, magnesium hydroxide, simeticone), cimetidine, NSAIDs, antibiotics and oral hypoglycaemic medicines.

Indeed, interaction studies conducted with some drugs have shown no influence on the pharmacokinetics of amlodipine:

- co-administration of amlodipine with cimetidine does not alter the pharmacokinetics of amlodipine.
- when sildenafil and amlodipine are used in combination, each one independently exerts its own blood pressure lowering effect.
- grapefruit juice: co-administration of 240 ml of grapefruit juice with a single oral dose of 10mg amlodipine in 20 healthy volunteers has no significant effect on the pharmacokinetics of amlodipine.

Moreover, interaction studies conducted with some drugs have shown that amlodipine has no influence on their pharmacokinetics parameters:

- atorvastatin: co-administration of multiple doses of 10mg amlodipine with 80mg of atorvastatin does not cause a significant change in the pharmacokinetics parameters of atorvastatin.
- digoxin: co-administration of amlodipine with digoxin does not change serum digoxin levels or digoxin renal clearance in healthy volunteers.
- warfarin: in healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co administration of amlodipine with warfarin does not change the warfarin prothrombin response time.
- ciclosporin: Pharmacokinetic studies with ciclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciclosporin

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 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.

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 nursing or to discontinue Coveram 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 “*Special warnings and precautions for use*”). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections “*Contraindications*” and “*Special warnings and precautions for use*”).

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 inhibitors 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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section “*Preclinical safety data*”). Should exposure to ACE inhibitors 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 “*Contraindications*” and “*Special warnings and precautions for use*”).

Linked to amlodipine

Data on a limited number of exposed pregnancies do not indicate that amlodipine and other calcium receptor antagonists have a harmful effect on the health of the foetus. However, there may be a risk of prolonged delivery.

Animal studies have not shown teratogenic effect (see section “*preclinical safety data*”).

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 better 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 with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. A decision on whether to continue/discontinue 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

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been reported in some patients treated by calcium channel blockers.

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. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

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, diarrhoea, constipation, pruritus, 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	Perindopril
Infections and infestations	Rhinitis	Uncommon	Very rare
	Eosinophilia	-	Uncommon*
Blood and the lymphatic System Disorders	Leukopenia/neutropenia (see section “ <i>Special warnings and precautions for use</i> ”)	Very rare	Very rare
	Agranulocytosis or pancytopenia (see section “ <i>Special warnings and precautions for use</i> ”)	-	Very rare
	Thrombocytopenia (see section “ <i>Special warnings and precautions for use</i> ”)	Very rare	Very rare
	Haemolytic anaemia enzyme specific in patients with a congenital deficiency of G-6PDH (see section “ <i>Special warnings and precautions for use</i> ”)	-	Very rare
Immune System Disorders	Hypersensitivity	Very rare	Uncommon
Metabolism and Nutrition Disorders	Hypoglycaemia (see sections “ <i>special warnings and precautions for use</i> ” and “ <i>Interaction with other medicinal products and other forms of interaction</i> ”)	-	Uncommon*
	Hyperkalaemia, reversible on discontinuation (see section “ <i>special warnings and precautions for use</i> ”)	-	Uncommon*
	Hyponatraemia	-	Uncommon*
	Hyperglycaemia	Very rare	-
Psychiatric disorders	Insomnia	Uncommon	-
	Mood altered (including anxiety)	Uncommon	Uncommon
	Depression	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	-
	Hypoesthesia	Uncommon	-
	Paraesthesia	Uncommon	Common
	Syncope	Uncommon	Uncommon*
	Confusional state	Rare	Very rare
	Hypertonia	Very rare	-
Neuropathy peripheral	Very rare	-	
Eye Disorders	Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see section “ <i>special warnings and precautions for use</i> ”)	-	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 “ <i>Special warnings and precautions for use</i> ”)	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section “ <i>Special warnings and precautions for use</i> ”)	Very rare	Very rare
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Uncommon	Very rare
Vascular Disorders	Flushing	Common	-
	Hypotension (and effects related to hypotension)	Uncommon	Common
	Vasculitis	Very Rare	Uncommon*
	Raynaud’s phenomenon	-	Not known
Respiratory, Thoracic and Mediastinal Disorders	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 habits	Common	-
	Dry mouth	Uncommon	Uncommon
	Diarrhoea	Common	Common
	Constipation	Common	Common
	Pancreatitis	Very rare	Very rare
Gastritis	Very rare	-	

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	Perindopril
Hepato-biliary Disorders	Hepatitis, jaundice	Very rare	-
	Hepatitis either cytolytic or cholestatic (see section "Special warnings and precautions")	-	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 "Special warnings and precautions")	Very rare	Uncommon
	Erythema multiform	Very rare	Very rare
	Alopecia	Uncommon	-
	Purpura	Uncommon	-
	Skin discolouration	Uncommon	-
	Hyperhidrosis	Uncommon	Uncommon
	Pruritus	Uncommon	Common
	Rash, exanthema	Uncommon	Common
	Urticaria (see section "Special warnings and precautions")	Uncommon	Uncommon
	Photosensitivity reactions	Very rare	Uncommon*
	Pemphigoid	-	Uncommon*
	Psoriasis aggravation	-	Rare
	Stevens-Johnson Syndrome	Very rare	-
	Exfoliative dermatitis	Very rare	-
Musculoskeletal and Connective Tissue Disorders	Toxic epidermal necrolysis	Not known	-
	Joint swelling (ankle swelling)	Common	-
	Arthralgia	Uncommon	Uncommon*
	Myalgia	Uncommon	Uncommon*
	Muscle spasms	Common	Common
	Back pain	Uncommon	-
Renal and Urinary Disorders	Micturition disorder, nocturia, pollakiuria	Uncommon	-
	Renal failure	-	Uncommon
	Renal failure acute	-	Very rare
Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon	Uncommon
	Gynaecomastia	Uncommon	-
General Disorders and Administration Site Condition	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 calculated from clinical trials for adverse events detected from spontaneous report

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

Additional information concerning amlodipine

Exceptional cases of extrapyramidal syndrome have been reported with calcium inhibitor treatment.

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 PUSAT FARMAKOVIGILANS-BPOM: Tlp. 021-4245459, 021-4244755 Ext. 111, Fax. 021-4243605, 021-42885404; Email: pv-center@pom.go.id and/or Indonesia-MESO-BadanPOM@hotmail.com.

OVERDOSE

There is no information on overdosage with Coveram 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 overdosage in humans. Symptoms associated with the overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

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

PHARMACOLOGICAL PROPERTIES

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 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 8mg perindopril tert-butylamine (equivalent to 10mg 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 8mg perindopril tert-butylamine (equivalent to 10mg 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 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:

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 relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and 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 dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of 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 suitable for use in patients with asthma, diabetes, and gout.

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10mg/d (calcium channel blocker) or lisinopril 10-40mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25mg/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 prior to enrollment or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette 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).

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. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours. As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

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

Distribution

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

Elimination

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

Elderly, Heart Failure, Renal Failure

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure (see section "Posology and method of administration"). 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 "Posology and method of administration" and "Special warnings and special precautions for use").

Amlodipine

Absorption, distribution, plasma protein binding

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

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. About 60% of the administered dose is excreted in the urine, 10% as unchanged amlodipine.

Elderly

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 "Posology and method of administration").

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

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. 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

Toxicological studies in animal reveal no special hazards for humans regarding safety pharmacology, genotoxicity, carcinogenicity, fertility and studies with repeated dosing. Reproductive toxicology studies in rats showed a prolonged duration of pregnancy and an increase in peri and postnatal mortality.

STORAGE CONDITIONS

Store below 30°C.

Shelf-life: 3 years.

PACK SIZES

COVERAM 5mg / 5mg Reg. No.: DK11631600710A1
- Box of 1 Pp. containers of 30 tablets.

COVERAM 5mg / 10mg Reg. No.: DK11631600710C1
- Box of 1 Pp. containers of 30 tablets.

COVERAM 10mg / 5mg Reg. No.: DK11631600710D1
- Box of 1 Pp. containers of 30 tablets.

COVERAM 10mg / 10mg Reg. No.: DK11631600710B1
- Box of 1 Pp. containers of 30 tablets.

ON MEDICAL PRESCRIPTION ONLY

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