



**Perindopril (as arginine) + Amlodipine (as besilate)**

- COVERAM® 5 mg / 5 mg Tablet**
- COVERAM® 5 mg / 10 mg Tablet**
- COVERAM® 10 mg / 5 mg Tablet**
- COVERAM® 10 mg / 10 mg Tablet**

**ANTIHYPERTENSIVE/ANTI-CAD**

**DESCRIPTION:**

**Coveram 5 mg/5 mg:** White, rod-shaped tablet engraved with 5/5 on one face and on the other face.  
**Coveram 5 mg/10 mg:** White, square-shaped tablet engraved with 5/10 on one face and on the other face.  
**Coveram 10 mg/5 mg:** White, triangular-shaped tablet engraved with 10/5 on one face and on the other face.  
**Coveram 10 mg/10 mg:** White, round tablet engraved with 10/10 on one face and on the other face.

**FORMULATION:**

**Coveram 5 mg/5 mg:** One tablet contains 3.395 mg perindopril equivalent to 5 mg perindopril arginine and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.  
**Coveram 5 mg/10 mg:** One tablet contains 3.395 mg perindopril equivalent to 5 mg perindopril arginine and 13.870 mg amlodipine besilate equivalent to 10 mg amlodipine.  
**Coveram 10 mg/5 mg:** One tablet contains 6.790 mg perindopril equivalent to 10 mg perindopril arginine and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.  
**Coveram 10 mg/10 mg:** 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.

**PHARMACODYNAMICS AND PHARMACOKINETICS:**

**Pharmacodynamics:**

**Perindopril:** Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (*e.g.* cough). Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity *in vitro*.

**Amlodipine:** Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow 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 ischemic 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 ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

**Pharmacokinetics:**

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. 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.

**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. *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 metabolized 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%.

**INDICATION:**

Perindopril arginine + Amlodipine besilate (**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.

**DOSAGE AND 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 Perindopril arginine + Amlodipine besilate (COVERAM) could be modified or individual titration with free combination may be considered.

**Special populations:**

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

Perindopril arginine + Amlodipine besilate (COVERAM) can be administered in patients with  $Cl_{cr} \geq 60$  ml/min, and is not suitable for patients with  $Cl_{cr} < 60$  ml/min. In these patients, an individual dose titration with the monocomponents is recommended.

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 dialyzable.

**Hepatic impairment:** 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. 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.

**Pediatric population:** Perindopril arginine + Amlodipine besilate (COVERAM) should not be used in children and adolescents as the efficacy and tolerability of perindopril and amlodipine, 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,
- Concomitant use of Perindopril arginine + Amlodipine besilate (COVERAM) with aliskiren-containing products in patients with diabetes mellitus or renal impairment ( $GFR < 60$  ml/min/1.73 m<sup>2</sup>),

GENERAL INFORMATIONS		NUMBER PAGES	
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- Concomitant use with sacubitril/valsartan therapy. Perindopril arginine + Amlodipine besilate (COVERAM) must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan,
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces,
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney.

**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),
- Hemodynamically unstable heart failure after acute myocardial infarction.

**Linked to Perindopril arginine + Amlodipine besilate (COVERAM):**  
All contraindications related to each monocomponent, as listed above, should apply also to the fixed combination of Perindopril arginine + Amlodipine besilate (COVERAM).

- Hypersensitivity to any of the excipients.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE:**

All warnings related to each monocomponent, as listed below, should apply also to the fixed combination of Perindopril arginine + Amlodipine besilate (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. This may occur at any time during therapy. In such cases, Perindopril arginine + Amlodipine besilate (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 edema 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.

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.

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. 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. 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). 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:**

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 desensitization:**

Patients receiving ACE inhibitors during desensitization 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/Anemia:**

Neutropenia/agranulocytosis, thrombocytopenia and anemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. 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. 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, hyperkalemia 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.

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, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

**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, diarrhea or vomiting, or who have severe renin-dependent hypertension. In patients at high risk of symptomatic hypotension, blood pressure, renal function and serum potassium should be monitored closely during treatment with Perindopril arginine + Amlodipine besilate (COVERAM). Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

**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.

Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment. 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.

**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 states in the black hypertensive population.

**Cough:**

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

**Surgery/Anesthesia:**

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Perindopril arginine + Amlodipine besilate (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. ACE inhibitors can cause hyperkalemia 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 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, cotrimoxazole 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 appropriate, they should be used with caution and with frequent monitoring of serum potassium.

#### **Diabetic patients:**

In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with an ACE inhibitor.

#### **Linked to amlodipine:**

##### **Precautions for use**

The safety and efficacy of amlodipine in hypertensive crisis has 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 edema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

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

##### **Elderly:**

In the elderly, increase of the dosage should take place with care.

##### **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 dialyzable.

#### **Linked to Perindopril arginine + Amlodipine besilate (COVERAM):**

All warnings related to each monocomponent, as listed above, should apply also to the fixed combination of Perindopril arginine + Amlodipine besilate (COVERAM).

##### **Precautions for use**

##### **Excipients:**

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the total lactase deficiency should not take this medicinal product.

##### **Interactions:**

The concomitant use of Perindopril arginine + Amlodipine besilate (COVERAM) with lithium, potassium-sparing drugs or potassium supplements, or dantrolene is not recommended.

##### **Effects on ability to drive and use machines**

No studies on the effects of Perindopril arginine + Amlodipine besilate (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 suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. Caution is recommended especially at the start of treatment.

#### **PREGNANCY AND LACTATION:**

Given the effects of the individual components in this combination product on pregnancy and lactation: Perindopril arginine + Amlodipine besilate (COVERAM) is not recommended during the first trimester of pregnancy. It is contraindicated during the second and third trimesters of pregnancy.

Perindopril arginine + Amlodipine besilate (COVERAM) is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Perindopril arginine + Amlodipine besilate (COVERAM) 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. The use of ACE inhibitors is contraindicated during the second and third trimesters of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small

increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension.

##### **Linked to amlodipine**

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

In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.

##### **Breastfeeding:**

##### **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:**

##### **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.

#### **INTERACTIONS:**

##### **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, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

##### **Drugs increasing the risk of angioedema:**

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema. 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.

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.

##### **Drugs inducing hyperkalemia:**

Although serum potassium usually remains within normal limits, hyperkalemia may occur in some patients treated with Perindopril arginine + Amlodipine besilate (COVERAM). Some drugs or therapeutic classes may increase the occurrence of hyperkalemia: 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 hyperkalemia. Therefore, the combination of Perindopril arginine + Amlodipine besilate (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 contraindicated:**

##### **Aliskiren:**

In diabetic or impaired renal patients, risk of hyperkalemia, 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 hemofiltration 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. 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:**

##### **Aliskiren:**

In patients other than diabetic or impaired renal patients, risk of hyperkalemia, 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, hyperkalemia, 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 edema (angioedema).

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

Hyperkalemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalemic effects). The combination of perindopril with the above-mentioned drugs is not recommended. 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.

**Concomitant use which requires special care:**

Antidiabetic agents (insulins, oral hypoglycemic agents): Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycemia. 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 12.5 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, risk of hyperkalemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.

Before initiating the combination, check the absence of hyperkalemia and renal impairment. A close monitoring of the kalemia and creatininemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

**Non-steroidal anti-inflammatory Drugs (NSAIDs) including acetylsalicylic acid  $\geq$  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:**

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 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 regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (*e.g.* rifampicin, 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 exposure. 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 patients is recommended when amlodipine is co administered with clarithromycin.

**Concomitant use to be taken into consideration:**

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 a patient 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. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

**Cyclosporine:**

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

**Simvastatin:**

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

**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 (Perindopril arginine + Amlodipine besilate)**

**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/anesthetics: increased antihypertensive effect and increased risk of orthostatic hypotension.

**ADVERSE DRUG REACTIONS:**

**a. Summary of safety profile**

The most commonly reported adverse reactions with perindopril and amlodipine given separately are: edema, somnolence, dizziness, headache (especially at the beginning of the treatment), dysgeusia, paresthesia, visual impairment (including diplopia), tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), dyspnea, cough, abdominal pain, nausea, vomiting, dyspepsia, change of bowel habit, diarrhea, 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 ( $\geq$ 1/10); common ( $\geq$ 1/100 to <1/10); uncommon ( $\geq$ 1/1000 to <1/100); rare ( $\geq$ 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
<b>Infections and infestations</b>	Rhinitis	Uncommon	Very rare
<b>Blood and the lymphatic System Disorders</b>	Eosinophilia	-	Uncommon*
	Leukopenia/neutropenia	Very rare	Very rare
	Agranulocytosis or pancytopenia	-	Very rare
	Thrombocytopenia	Very rare	Very rare
<b>Immune System Disorders</b>	Hemolytic anemia enzyme specific in patients with a congenital deficiency of G-6PDH	-	Very rare
	Hypersensitivity	Very rare	Uncommon
<b>Metabolism and Nutrition Disorders</b>	Hypoglycemia	-	Uncommon*
	Hyperkalemia, reversible on discontinuation	-	Uncommon*
	Hyponatremia	-	Uncommon*
<b>Psychiatric disorders</b>	Hyperglycemia	Very rare	-
	Insomnia	Uncommon	-
	Mood altered (including anxiety)	Uncommon	Uncommon
	Depression	Uncommon	-
<b>Nervous System disorders</b>	Sleep disorder	-	Uncommon
	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	-
	Paresthesia	Uncommon	Common
	Syncope	Uncommon	Uncommon*
	Confusional state	Rare	Very rare
	Hypertonia	Very rare	-
	Neuropathy peripheral	Very rare	-
<b>Eye Disorders</b>	Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients	-	Very rare
	Extrapyramidal disorder (extrapyramidal syndrome)	Not known	-
<b>Ear and labyrinth disorders</b>	Visual impairment	Common	Common
	Diplopia	Common	-
<b>Cardiac Disorders</b>	Tinnitus	Uncommon	Common
	Vertigo	-	Common
	Palpitations	Common	Uncommon*
<b>Vascular Disorders</b>	Tachycardia	-	Uncommon*
	Angina pectoris	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients	Very rare	Very rare
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Uncommon	Very rare
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	Flushing	Common	-
	Hypotension (and effects related to hypotension)	Very Rare	Common
	Vasculitis	Very Rare	Uncommon*
<b>Gastro-intestinal Disorders</b>	Raynaud's phenomenon	-	Not known
	Dyspnea	Common	Common
	Cough	Uncommon	Common
	Bronchospasm	-	Uncommon
<b>Skin and Subcutaneous Tissue Disorders</b>	Eosinophilic pneumonia	-	Very rare
	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
	Diarrhea	Common	Common
	Constipation	Common	Common
	Pancreatitis	Very rare	Very rare
	Gastritis	Very rare	-
	<b>Musculoskeletal and Connective Tissue Disorders</b>	Hepatitis, jaundice	Very rare
Hepatitis either cytolytic or cholestatic		-	Very rare
Hepatic enzymes increased (mostly consistent with cholestasis)		Very rare	-
Quincke's edema		Very rare	-
Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx		Very rare	Uncommon
Erythema multiforme		Very rare	Very rare
Alopecia		Uncommon	-
Purpura		Uncommon	-
Skin discoloration		Uncommon	-
Hyperhidrosis		Uncommon	Uncommon
Pruritus		Uncommon	Common
Rash, exanthema		Uncommon	Common
Urticaria		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	-	
<b>Renal and Urinary Disorders</b>	Joint swelling (ankle swelling)	Common	-
	Arthralgia	Uncommon	Uncommon*
	Myalgia	Uncommon	Uncommon*
	Muscle spasms	Common	Common
<b>Reproductive System and Breast Disorders</b>	Back pain	Uncommon	-
	Micturition disorder, nocturia, pollakiuria	Uncommon	-
	Renal failure	-	Uncommon
<b>Reproductive System and Breast Disorders</b>	Renal failure acute	-	Very rare
	Erectile dysfunction	Uncommon	Uncommon
<b>Reproductive System and Breast Disorders</b>	Gynecomastia	Uncommon	-



MedDRA System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	Perindopril
General Disorders and Administration Site Conditions	Edema	Very common	-
	Edema peripheral	-	Uncommon*
	Fatigue	Common	-
	Chest pain	Uncommon	Uncommon*
	Asthenia	Common	Common
	Pain	Uncommon	-
	Malaise	Uncommon	Uncommon*
Investigations	Pyrexia	-	Uncommon*
	Weight increased, weight decreased	Uncommon	-
	Blood urea increased	-	Uncommon*
	Blood creatinine increased	-	Uncommon*
	Blood bilirubin increase	-	Rare
	Hepatic enzyme increase	-	Rare
Injury, poisoning and procedural complications	Hemoglobin decreased and hematocrit decreased	-	Very rare
	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.

**REPORTING OF ADVERSE DRUG REACTION:**

For suspected adverse drug reaction, report to the FDA at [www.fda.gov/ph](http://www.fda.gov/ph)

Seek medical attention immediately at the first sign of any adverse drug reaction.

**OVERDOSE AND TREATMENT:**

There is no information on overdose with Perindopril arginine + Amlodipine besilate (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 vasodilation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

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

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

Gastric lavage may be worthwhile in some cases. 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 the overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position.

If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril can be removed from the systemic circulation by hemodialysis.

Pacemaker therapy is indicated for treatment-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

**MISSED DOSE:**

It is important to take the medicine everyday as regular treatment works better. However, if a dose is forgotten, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

**DISCONTINUATION OF TREATMENT:**

As the treatment with Perindopril arginine + Amlodipine besilate (COVERAM) is usually life-long, patient should discuss with the doctor before stopping the treatment.

**STORAGE CONDITION:**

Keep out of the reach and site of children.

Do not use Perindopril arginine + Amlodipine besilate (COVERAM) after the expiry date which is stated on the carton and bottle. The expiry date refers to the last day of that month. Keep the bottle tightly closed in order to protect from moisture. Store in the original package.

Store at temperatures not exceeding 30°C.

**CAUTION:**

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

**PACKAGING:**

Coveram 5mg/5mg, 5mg/10mg, 10mg/5mg and 10mg/10mg: 30 tablets in polypropylene container equipped with a low density polyethylene flow reducer and a low density polyethylene stopper containing a desiccant gel.



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