COVERAM 5 mg / 5 mg tablets

COVERAM 5 mg / 10 mg tablets

COVERAM 10 mg / 5 mg tablets

COVERAM 10 mg / 10 mg tablets

COMPOSITION

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.

PHARMACEUTICAL FORM

Tablet.

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

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

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

COVERAM 10 mg / 10 mg
White, round tablet, 8.5 mm diameter, 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.

POSOLOGY 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

Renal impairment and elderly (see section "Special warnings and precautions for use" and "Pharmacokinetic properties")
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.

Coveram can be administered in patients with Clcr ≥ 60ml/min, and is not suitable for patients with Clcr < 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.

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 population
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 therapy. Coveram must not be initiated earlier than 36 hours after the last dose of 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 the active substance or to dihydropyridines derivatives,
- Shock, including cardiogenic shock,
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis),
- Haemodynamically unstable heart failure after acute myocardial infarction.

Linked to Coveram:
All contraindications related to each monocomponent, as listed above, should apply also to the fixed combination of Coveram.
- Hypersensitivity to any of the excipients.

DISETUJUI OLEH BPOM : 27/02/2023

ID REG : EREG100087VR12300017
EREG100087VR12300027
EREG100087VR12300028
EREG100087VR12300029

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Linked to perindopril

Special warnings

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril *(see section "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 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 ACE inhibitors with NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section *"Interaction with other medicinal products and other forms of interaction"*).
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 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, treatment 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 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 impairement:

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 states in the black hypertensive population.

Cough:

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

Surgery/Anaesthesia:

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, 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.

Hyperkalaemia:

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril, ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydratation, 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) 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 (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
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 oedema was higher in the amlodipine treated group than in the placebo group (see section *"Pharmacodynamic properties"*). 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 (see sections *"Posology and method of administration"* and *"Pharmacokinetic properties"*).

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

Linked to Coveram

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

Precautions for use

Excipients:

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 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 increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see sections *"Contraindication"* and *"Special warnings and precautions for use"*). Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections *"Contraindication"* and *"Special warnings and precautions for use"*). Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk for angioedema (see section *"Special warnings and precautions for use"*).

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

Concomitant use contra-indicated (see section *"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 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Concomitant use not recommended (see section *"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).

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 12.5 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 hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.
Before initiating the combination, check the absence of hyperkalaemia and renal impairment.
A close monitoring of the kalaemia and creatininemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including *acetylsalicylic acid* ≥ 3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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.

Ciclosporine:

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

Simvastatin:

- Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin 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.
- In monotherapy, amlodipine has been safely administered with thiazide diuretics, sildenafil, anti-acid medicines (aluminium hydroxide gel, magnesium hydroxide, simeticone), cimetidine, NSAIDs, antibiotics and oral hypoglycaemic medicines.
- Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Linked to Coveram:

Concomitant use which requires special care*:*

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

Concomitant use to be taken into consideration*:*

- . **Antihypertensive agents (such as beta-blockers) and vasodilatators**:
  Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine. Concomitant use with nitroglycerine and other nitrates or other vasodilatators, 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 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 trimesters 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 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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section *"Preclinical safety data"*). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections *"Contraindications"* and *"Special warnings and precautions for use"*).

Linked to amlodipine
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses (see section "Preclinical safety data").Use in pregnancy is only recommended when there is no safer alternative and *when* the *disease itself carries greater risk for* the *mother and* foetus.

Breast-feeding:
Linked to perindopril

Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with 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 (see section *"Preclinical safety data"*).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

UNDESIRABLE EFFECTS

a. Summary of safety profile

The most commonly reported adverse reactions with perindopril and amlodipine given separately are: oedema, somnolence, dizziness, headache (especially at the beginning of the treatment), dysgeusia, paraesthesia, visual impairment (including diplopia), tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), dyspnoea, cough, abdominal pain, nausea, vomiting, dyspepsia, change of bowel habit, diarrheoa, constipation, pruritt, 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
Blood and the lymphatic System Disorders	Eosinophilia	-	Uncommon*
	Leukopenia/neutropenia (see section "*Special warnings and precautions for use*")	Very rare	Very rare
	Agranulocytosis or pancytopenia (see section "*Special warnings and precautions for use*")	-	Very rare
	Thrombocytopenia (see section "*Special warnings and precautions for use*")	Very rare	Very rare
	Haemolytic anaemia enzyme specific in patients with a congenital deficiency of G-6PDH (see section "*Special warnings and precautions for use*")	-	Very rare
Immune System Disorders	Hypersensitivity	Very rare	Uncommon
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH	-	Rare
Metabolism and Nutrition Disorders	Hypoglycaemia (see sections *"special warnings and precautions for use"* and *"Interaction with other medicinal products and other forms of interaction"*)	-	Uncommon*
	Hyperkalaemia, reversible on discontinuation (see section *"special warnings and precautions for use"*)	-	Uncommon*
	Hyponatraemia	-	Uncommon*
	Hyperglycaemia	Very rare	-
Psychiatric disorders	Insomnia	Uncommon	-
	Mood altered (including anxiety)	Uncommon	Uncommon
	Depression	Uncommon	Uncommon*
	Sleep disorder	-	Uncommon
Nervous System disorders	Somnolence (especially at the beginning of the treatment)	Common	Uncommon*
	Dizziness (especially at the beginning of the treatment)	Common	Common
	Headache (especially at the beginning of the treatment)	Common	Common
	Dysgeusia	Uncommon	Common
	Tremor	Uncommon	-
	Hypoaesthesia	Uncommon	-
	Paraesthesia	Uncommon	Common
	Syncope	Uncommon	Uncommon*
	Confusional state	Rare	Very rare
	Hypertonia	Very rare	-
	Neuropathy peripheral	Very rare	-
	Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see section *"special warnings and precautions for use"*)	-	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 *"Special warnings and precautions for use"*)	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section *"Special warnings and precautions for use"*)	Very rare	Very rare
	Arrythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Uncommon	Very rare
Vascular Disorders	Flushing	Common	Rare*
	Hypotension (and effects related to hypotension)	Uncommon	Common
	Vasculitis	Very Rare	Uncommon*
	Raynaud's phenomenon	-	Not known
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Common	Common
	Cough	Uncommon	Common
	Bronchospasm	-	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastro-intestinal Disorders	Gingival hyperplasia	Very rare	-
	Abdominal pain	Common	Common
	Nausea	Common	Common
	Vomiting	Uncommon	Common
	Dyspepsia	Common	Common
	Change of bowel habit	Common	-
	Dry mouth	Uncommon	Uncommon
	Diarrheoa	Common	Common
	Constipation	Common	Common
	Pancreatitis	Very rare	Very rare
	Gastritis	Very rare	-
Hepato-biliary Disorders	Hepatitis, jaundice	Very rare	-
	Hepatitis either cytolitic or cholestatic (see section *"Special warnings and precautions"*)	-	Very rare

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MedDRA System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	Perindopril
	Hepatic enzymes increased (mostly consistent with cholestasis)	Very rare	-
Skin and Subcutaneous Tissue Disorders	Quincke's oedema Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section *"Special warnings and precautions"*)	Very rare Very rare	- Uncommon
	Erythema multiform	Very rare	Very rare
	Alopecia	Uncommon	-
	Purpura	Uncommon	-
	Skin discolouration	Uncommon	-
	Hyperhidrosis	Uncommon	Uncommon
	Prurit	Uncommon	Common
	Rash, exanthema	Uncommon	Common
	Urticaria (see section *"Special warnings and precautions"*)	Uncommon	Uncommon
	Photosentivity reactions	Very rare	Uncommon*
	Pemphigoid	-	Uncommon*
	Psoriasis aggravation	-	Rare
	Stevens-Johnson Syndrome	Very rare	-
	Exfoliative dermatitis	Very rare	-
	Toxic epidermal necrolysis	Not known	-
Musculoskeletal and Connective Tissue Disorders	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
	Acute renal failure	-	Rare
	Anuria/Oliguria	-	Rare*
Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon	Uncommon
	Gynaecomastia	Uncommon	-
General Disorders and Administration Site Conditions	Oedema	Very common	-
	Oedema peripheral	-	Uncommon*
	Fatigue	Common	-
	Chest pain	Uncommon	Uncommon*
	Asthenia	Common	Common
	Pain	Uncommon	-
	Malaise	Uncommon	Uncommon*
	Pyrexia	-	Uncommon*
Investigations	Weight increased, weight decreased	Uncommon	-
	Blood urea increased	-	Uncommon*
	Blood creatinine increased	-	Uncommon*
	Blood bilirubin increase	-	Rare
	Hepatic enzyme increase	-	Rare
	Haemoglobin decreased and haematocrit decreased	-	Very rare
Injury, poisoning and procedural complications	Fall	-	Uncommon*

* Frequency calculated from clinical trials for adverse events detected from spontaneous report

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.
Symptoms: available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

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

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

Stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.
Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) (n=6110) or placebo (n=6108).
The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.
The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).
In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

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 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.

Treatment to prevent heart attack trial (ALLHAT):
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 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.
A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke > 6 months prior to enrollment or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), 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. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/Elimination

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

Elderly

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. *Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied*.

Hepatic impairment

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

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:

Reproductive toxicology

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

Impairment of fertility

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

- Carcinogenesis, mutagenesis

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

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

* Based on patient weight of 50 kg

STORAGE CONDITIONS

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

Shelf-life : 3 years.

PACK SIZES

COVERAM 5 mg / 5 mg Reg. No. : DKI1631600710A1
- Box of 1 Pp. containers of 30 tablets.

COVERAM 5 mg / 10 mg Reg. No. : DKI1631600710C1
- Box of 1 Pp. containers of 30 tablets.

COVERAM 10 mg / 5 mg Reg. No. : DKI1631600710B1
Box of 1 Pp. containers of 30 tablets.

COVERAM 10 mg / 10 mg Reg. No. : DKI1631600710D1
- Box of 1 Pp. containers of 30 tablets.

ON MEDICAL PRESCRIPTION ONLY

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Les Laboratoires Servier - France

SERVIER

Manufactured by :
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INFORMASI PRODUK UNTUK PASIEN

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

Bacalah seluruh bagian leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini, karena leaflet ini berisi informasi yang penting bagi Anda.
- Simpanlah leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, konsultasikan kepada dokter, apoteker atau perawat Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Hal ini dapat membahayakan orang lain, meskipun gejala penyakitnya sama dengan Anda.
- Jika Anda mengalami efek samping, konsultasikan kepada dokter, apoteker, atau perawat Anda. Termasuk efek samping yang tidak tercantum dalam leaflet ini. Lihat Bagian 4.

Apakah isi leaflet ini?

1. Apakah Coveram itu, dan apa kegunaannya

Coveram diresepkan untuk pengobatan tekanan darah tinggi (hipertensi) dan/atau pengobatan penyakit arteri koroner yang stabil (suatu kondisi di mana suplai darah ke jantung berkurang atau tersumbat).
Pasien yang sudah menggunakan perindopril dan amlodipine dari tablet terpisah dapat menerima satu tablet Coveram yang mengandung kedua bahan tersebut.

Coveram adalah kombinasi dari dua bahan aktif, perindopril dan amlodipine.
Perindopril adalah penghambat ACE (angiotensin converting enzyme). Amlodipine adalah antagonis kalsium (yang termasuk dalam kelas obat yang disebut dihydropyridines). Bersama-sama mereka bekerja untuk melebarkan dan mengendurkan pembuluh darah sehingga darah melewatinya lebih mudah dan memudahkan jantung Anda untuk mempertahankan aliran darah yang baik.

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan Coveram

Jangan menggunakan Coveram
- jika Anda alergi terhadap perindopril atau penghambat ACE lainnya, atau terhadap amlodipine atau antagonis kalsium lainnya, atau bahan lain yang terkandung dalam obat ini,
- jika Anda sedang hamil lebih dari 3 bulan (lebih baik untuk menghindari konsumsi Coveram di masa awal kehamilan – lihat Bagian Hamil),
- jika Anda mengalami gejala seperti mengi (napas berbunyi karena penyempitan saluran pernapasan), pembengkakan pada wajah atau lidah, muncul rasa gatal yang hebat atau kemerahan (ruam) yang parah pada kulit pada penggunaan penghambat ACE sebelumnya, atau jika Anda atau anggota keluarga Anda mengalami gejala-gejala ini dalam keadaan lainnya (suatu kondisi yang disebut angioedema),
- jika Anda memiliki diabetes dan kerusakan fungsi ginjal dan Anda dirawat dengan obat penurun tekanan darah obat yang mengandung aliskiren,
- jika Anda memiliki penyempitan katup aorta jantung (stenosis aorta) atau cardiogenic shock (suatu kondisi dimana jantung Anda tidak dapat mensuplai darah ke tubuh),
- jika Anda memiliki tekanan darah rendah yang parah (hipotensi),
- jika Anda menderita gagal jantung setelah mengalami serangan jantung,

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- jika Anda menjalani dialysis atau jenis penyaringan darah yang lain. Tergantung pada mesin yang digunakan, Coveram mungkin tidak cocok untuk Anda,
- jika Anda memiliki masalah ginjal di mana suplai darah ke ginjal Anda berkurang (stenosis arteri ginjal),
- jika Anda telah atau sedang menggunakan sacubitril/valsartan, obat untuk gagal jantung, karena risiko angioedema (pembengkakan cepat di bawah kulit di area seperti tenggorokan) meningkat (lihat "Peringatan dan Tindakan Pencegahan " dan "Obat-obat lainnya dan Coveram").

Peringatan dan perhatian

Jika Anda mengalami kondisi di bawah ini, konsultasikan dengan dokter atau apoteker Anda sebelum minum Coveram:
- kardiomiopati hipertrofik (penyakit otot jantung) atau stenosis arteri ginjal (penyempitan arteri yang memasok darah ke ginjal),
- gagal jantung
- peningkatan tekanan darah yang parah (krisis hipertensi),
- masalah jantung lainnya,
- masalah hati
- memiliki penyakit ginjal atau Anda sedang menjalani dialisis,
- mengalami peningkatan abnormal kadar hormon yang disebut aldosteron dalam darah Anda (aldosteronisme primer),
- menderita penyakit kolagen (penyakit kulit) seperti lupus eritematosus sistemik atau skleroderma,
- diabetes,
- sedang melakukan diet untuk membatasi kadar garam atau menggunakan pengganti garam yang mengandung kalium (keseimbangan kandungan kalium dalam darah sangat penting),
- jika Anda sudah tua dan dosis Anda perlu ditingkatkan,
- jika Anda sedang mengonsumsi obat-obatan berikut ini yang digunakan untuk mengobati tekanan darah tinggi:
  - suatu "angiotensin II receptor blocker" (ARBs) (juga dikenal sebagai sartans - misalnya valsartan, telmisartan, irbesartan), khususnya jika Anda memiliki penyakit ginjal terkait diabetes.
  - aliskiren.

  Dokter Anda mungkin memeriksa fungsi ginjal Anda, tekanan darah Anda, dan jumlah elektrolit (misalnya kalium) dalam darah Anda secara rutin.
  Lihat juga informasi yang berjudul "Jangan meminum Coveram".
- jika Anda sedang mengonsumsi obat-obatan berikut ini, resiko angiodema meningkat:
  - racecadotril (digunakan untuk mengobati diare),
  - sirolimus, everolimus, temsirolimus dan obat-obat lain yang termasuk dalam kelas yang disebut penghambat mTor (digunakan untuk menghindari penolakan organ yang ditransplantasikan dan untuk kanker),
  - sacubitril (tersedia sebagai kombinasi dosis tetap dengan valsartan), digunakan untuk mengobati gagal jantung jangka panjang,
  - linagliptin, saxagliptin, sitagliptin, vildagliptin dan obat-obat lain yang termasuk dalam golongan yang disebut gliptin (digunakan untuk mengobati diabetes)

<u>Angioedema</u>
Angioedema (reaksi alergi parah dengan pembengkakan wajah, bibir, lidah atau tenggorokan dengan kesulitan menelan atau bernapas) telah dilaporkan pada pasien yang diobati dengan ACE inhibitor, termasuk Coveram. Ini dapat terjadi kapan saja selama perawatan. Jika Anda mengalami gejala seperti itu, Anda harus berhenti mengonsumsi Coveram dan segera menemui dokter. Lihat juga bagian 4.

Anda harus memberitahukan kepada dokter Anda jika Anda merasa bahwa Anda sedang (atau mungkin menjadi) hamil. Coveram tidak dianjurkan untuk dikonsumsi pada awal kehamilan, dan tidak boleh diminum jika umur kehamilan Anda lebih dari 3 bulan, karena dapat menyebabkan bahaya yang serius terhadap bayi Anda jika digunakan pada tahap tersebut (lihat bagian "Kehamilan").

Ketika Anda meminum Coveram, Anda juga harus memberitahukan kepada dokter atau staf medis Anda:
- jika Anda akan menjalani anestesi dan/atau operasi,
- jika Anda baru saja menderita diare atau muntah,

- jika Anda akan menjalani LDL apheresis (yang merupakan pengangkatan kolesterol dari darah Anda dengan menggunakan mesin),
- jika Anda akan menjalani perawatan desensitisasi untuk mengurangi efek dari alergi terhadap sengatan lebah atau tawon.

Anak-anak dan remaja

Coveram tidak ditujukan untuk penggunaan pada anak-anak dan remaja.

Obat lain dan Coveram

Harap memberitahukan kepada dokter atau apoteker Anda jika Anda meminum, baru saja meminum atau mungkin meminum obat-obatan lainnya.

Anda harus menghindari untuk meminum Coveram dengan:
- lithium (digunakan untuk mengobati gangguan kesehatan mental seperti mania atau penyakit depresi),
- estramustine (digunakan dalam terapi kanker),
- obat hemat kalium (misalnya triamteren, amilorid), suplemen kalium atau kalium yang mengandung pengganti garam, obat-obat lain yang dapat meningkatkan kalium dalam tubuh Anda (seperti heparin, obat yang digunakan untuk mengencerkan darah untuk mencegah pembekuan; trimetoprim dan kotrimoksazol juga dikenal sebagai trimetoprim/sulfametoksazol untuk infeksi yang disebabkan oleh bakteri),
- obat hemat kalium yang digunakan dalam pengobatan gagal jantung: eplerenon dan spironolakton dengan dosis antara 12,5 mg sampai 50 mg per hari,

Pengobatan dengan Coveram dapat dipengaruhi oleh obat-obatan lainnya. Dokter Anda mungkin perlu mengubah dosis Anda dan/atau mengambil tindakan lainnya. Pastikan untuk memberitahukan kepada dokter Anda jika Anda sedang mengkonsumsi atau meminum obat-obatan berikut ini, karena perawatan khusus mungkin diperlukan:
- obat-obatan lainnya untuk mengobati tekanan darah tinggi, termasuk Angiotensin II Receptor Blocker (ARB), aliskiren (lihat juga informasi dengan judul "Jangan menggunakan Coveram" dan "Peringatan dan perhatian"), atau diuretik (obat yang meningkatkan jumlah urin yang diproduksi oleh ginjal),
- obat-obatan yang paling sering digunakan untuk mengobati diare (racecadotril) atau hindari penolakan organ yang ditransplantasikan (sirolimus, everolimus, temsirolimus dan obat-obat lain yang termasuk dalam kelas yang disebut penghambat mTor). Lihat informasi di bagian “Peringatan dan perhatian”,
- Sacubitril/valsartan (digunakan untuk mengobati gagal jantung jangka panjang). Lihat informasi di bagian “Jangan menggunakan Coveram" dan "Peringatan dan perhatian".
- Obat-obatan anti inflamasi non-steroid (contoh: ibuprofen) untuk menghilangkan rasa sakit, atau asam asetilsalisilat dosis tinggi, zat dalam obat-obatan yang digunakan untuk menghilangkan rasa sakit dan menurunkan demam, serta untuk mencegah pembekuan darah
- Obat-obatan untuk mengobati diabetes (seperti insulin),
- Obat-obatan untuk mengobati gangguan kesehatan mental seperti depresi, kecemasan, skizofrenia dan lain-lain (misalnya antidepresan trisiklik, antipsikotik, imipramine seperti antidepresan, neuroleptik),
- imunosupresan (obat-obatan yang mengurangi mekanisme pertahanan tubuh) digunakan untuk pengobatan gangguan auto-imun atau setelah operasi transplantasi (misalnya siklosporin, takrolimus),
- trimethoprim and Co-trimoxazole (untuk pengobatan infeksi),
- allopurinol (untuk pengobatan asam urat/gout),
- procainamide (untuk pengobatan detak jantung yang tidak teratur),
- vasodilator termasuk golongan nitrat (produk-produk yang dapat melebarkan pembuluh darah),
- efedrin, noradrenalin atau adrenalin (obat-obatan yang digunakan untuk pengobatan tekanan darah rendah, syok atau asma),
- baclofen atau dantrolen (infus), keduanya digunakan untuk mengobati otot kaku pada penyakit seperti sklerosis ganda; dantrolene juga digunakan untuk mengobati hipertermia ganas selama anestesi (gejalanya termasuk demam sangat tinggi dan otot kaku),
- beberapa antibiotik seperti rifampicin, erythromycin, clarithromycin (untuk infeksi yang disebabkan oleh bakteri),
- *Hypericum perforatum* (St John’s wort, suatu obat herbal yang digunakan untuk mengobati depresi)

- simvastatin (obat untuk menurunkan kolesterol),
- obat-obatan antiepilepsi seperti karbamazepin, fenobarbital, fenitoin, fosfenytoin, primidon,
- itrakonazol, ketokonazol (obat-obatan yang digunakan untuk infeksi yang disebabkan jamur),
- penghambat alfa yang digunakan untuk mengobati pembesaran prostat seperti prazosin, alfuzosin, doxazosin, tamsulosin, terazosin,
- amifostin (digunakan untuk mencegah atau mengurangi efek samping yang disebabkan oleh obat-obatan lain atau terapi radiasi yang digunakan untuk mengobati kanker),
- kortikosteroid (digunakan untuk berbagai kondisi termasuk asma yang berat dan artritis rheumatoid/peradangan sendi),
- garam-garam emas, terutama dengan pemberian melalui intravena (digunakan untuk mengobati gejala artritis rheumatoid/peradangan sendi),
- ritonavir, indinavir, nelfinavir (juga disebut penghambar enzim protease yang digunakan untuk mengobati HIV).

Coveram dengan makanan dan minuman

Coveram harus diminum sebelum makan.
Jus jeruk dan buah jeruk (*grapefruit*) sebaiknya tidak dikonsumsi oleh orang-orang yang sedang mengkonsumsi Coveram. Hal ini karena jus jeruk dan jeruk (*grapefruit*) dapat menyebabkan peningkatan kadar zat aktif amlodipin, yang dapat secara tidak terduga menyebabkan peningkatan tekanan darah sehingga menurunkan khasiat dari Coveram.

Hamil, menyusui dan kesuburan

Jika Anda sedang hamil atau menyusui, merencanakan untuk segera hamil atau berencana untuk memiliki bayi, berkonsultasilah dengan dokter atau apoteker Anda untuk memperoleh saran sebelum meminum atau mengkonsumsi obat ini.

Hamil
Anda harus memberitahukan kepada dokter Anda jika Anda merasa bahwa Anda (atau mungkin sedang) hamil. Dokter Anda biasanya akan menyarankan kepada Anda untuk berhenti meminum Coveram sebelum Anda hamil atau segera setelah Anda mengetahui bahwa Anda sedang hamil dan akan menyarankan kepada Anda agar meminum obat sebagai pengganti Coveram. Coveram tidak dianjurkan untuk diminum pada awal kehamilan, dan tidak boleh diminum ketika umur kehamilan lebih dari 3 bulan, karena dapat menyebabkan bahaya serius terhadap bayi Anda jika dikonsumsi setelah bulan ketiga kehamilan.

Menyusui
Amlodipin telah terbukti masuk ke dalam ASI dalam jumlah kecil. Katakan kepada dokter Anda jika Anda sedamg menyusui atau mulai menyusui. Coveram tidak dianjurkan bagi ibu yang sedang menyusui, dan dokter Anda dapat memilih pengobatan lainnya untuk Anda jika Anda ingin menyusui, terutama jika bayi Anda baru lahir, atau lahir prematur.

Mengemudi dan mengoperasikan mesin

Coveram dapat mempengaruhi kemampuan Anda untuk mengemudi atau mengoperasikan mesin. Jika tablet tersebut membuat Anda merasa sakit, pusing atau lelah, atau membuat Anda sakit kepala, jangan mengemudikan atau mengoperasikan mesin dan segera hubungi dokter Anda.

Coveram mengandung laktosa monohidrat

Jika Anda telah diberitahu oleh dokter Anda bahwa Anda memiliki intoleransi terhadap beberapa gula, hubungi dokter Anda sebelum meminum obat ini.

3. Bagaimana aturan pakai Coveram

Selalu minum obat ini sesuai dengan anjuran dokter atau apoteker Anda. Konsultasikan dengan dokter atau apoteker Anda jika Anda tidak merasa yakin.

Meminum tablet tersebut dengan segelas air, lebih baik di waktu yang sama di pagi hari, dan sebelum makan. Dokter Anda akan memutuskan mengenai dosis yang tepat bagi Anda. Tablet ini biasanya diminum satu tablet sekali sehari.

Coveram biasanya akan diresepkan untuk pasien yang sudah menggunakan perindopril dan amlodipine dari tablet terpisah.

Penggunaan pada anak-anak dan remaja
Penggunaan pada anak-anak dan remaja tidak dianjurkan.

Jika Anda menggunakan Coveram lebih dari seharusnya

Jika Anda meminum terlalu banyak tablet ini, segeralah mencari pertolongan medis dan hubungi bagian gawat darurat terdekat atau segera beri tahu dokter Anda. Efek yang paling mungkin terjadi jika overdosis adalah tekanan darah rendah yang dapat membuat Anda merasa pusing atau pingsan. Jika ini terjadi, berbaring dengan kaki terangkat dapat membantu.

Kelebihan cairan dapat menumpuk di paru-paru Anda (edema paru) menyebabkan sesak napas yang dapat berkembang hingga 24-48 jam setelah asupan.

Jika Anda lupa menggunakan Coveram

Adalah sangat penting untuk meminum obat Anda setiap hari sebagai pengobatan rutin adalah lebih efektif. Namun, Jika Anda lupa untuk meminum dosis Coveram, minumlah dosis berikutnya pada waktu seperti biasa biasa. Jangan meminum tablet tersebut dengan dosis ganda untuk menebus dosis (menggenapi/menambahkan) dosis yang lupa diminum.

Jika Anda berhenti menggunakan Coveram

Coveram sebagai pengobatan untuk tekanan darah tinggi biasanya diminum seumur hidup, Anda harus berkonsultasi dengan dokter Anda sebelum memutuskan untuk berhenti mengkonsumsi produk obat ini.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

4. Efek samping yang mungkin timbul

Sebagaimana semua obat-obatan pada umumnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Hentikan meminum produk obat dan **segera** kunjungi dokter Anda jika Anda mengalami salah satu dari efek samping berikut ini:

- tiba-tiba bersin, nyeri dada, sesak napas atau kesulitan bernafas,
- pembengkakan kelopak mata, wajah dan bibir,
- pembengkakan pada mulut, lidah dan tenggorokan yang menyebabkan kesulitan bernapas,
- reaksi kulit yang parah termasuk ruam kulit yang intens, gatal-gatal, kemerahan pada kulit pada seluruh tubuh Anda, gatal yang parah, melepuh, mengelupas dan pembengkakan kulit, radang selaput lendir (sindrom Stevens Johnson, Nekrolisis Epidermal Toksik) atau reaksi alergi lainnya,
- pusing berat atau pingsan,
- serangan jantung, detak jantung cepat atau abnormal yang tidak biasa, atau nyeri dada,
- mengalami peradangan pada pankreas yang dapat menyebabkan sakit perut dan sakit punggung yang parah disertai dengan perasaan sangat tidak enak.

Efek samping **umum** berikut telah dilaporkan. Jika salah satu dari efek samping ini menyebabkan Anda bermasalah, atau jika **berlangsung lebih dari satu minggu**, Anda harus **menghubungi dokter Anda**.

- Efek samping sangat lazim (dapat mempengaruhi lebih dari 1 orang dari 10 orang): edema (retensi cairan).

- Efek samping lazim (dapat mempengaruhi hingga 1 orang dari 10 orang):
  sakit kepala, pusing, mengantuk (terutama pada awal pengobatan), vertigo, mati rasa atau kesemutan pada anggota tubuh Anda, gangguan penglihatan (termasuk penglihatan ganda), tinnitus (sensasi suara di telinga), palpitasi (kesadaran detak jantung Anda), kemerahan, pusing karena tekanan darah rendah, batuk, sesak napas, mual (merasa sakit), muntah (sakit), sakit perut, gangguan rasa, dispepsia atau kesulitan pencernaan, perubahan kebiasaan buang air besar, diare, sembelit, reaksi alergi (seperti ruam kulit, gatal-gatal), kram otot, kelelahan, kelemahan, pembengkakan pergelangan kaki (edema perifer).

Efek samping lain yang telah dilaporkan termasuk daftar berikut. Jika salah satu dari ini menjadi serius, atau jika Anda melihat ada efek samping yang tidak tercantum dalam selebaran ini, beri tahu dokter atau apoteker Anda.

- Efek samping yang jarang (dapat mempengaruhi 1 dari 100 orang): perubahan suasana hati, kecemasan, depresi, sulit tidur, gangguan tidur, gemetar, pingsan, kehilangan sensasi nyeri, detak jantung tidak teratur, rinitis (hidung tersumbat atau meler), rambut rontok, bercak merah pada kulit, perubahan warna kulit, nyeri punggung, artralgia (nyeri sendi), mialgia (nyeri otot), nyeri dada, gangguan buang air kecil, peningkatan kebutuhan buang air kecil di malam hari, peningkatan frekuensi buang air kecil, nyeri, perasaan tidak sehat, bronkospasme (pengencangan dada, mengi dan sesak napas), mulut kering, angioedema (gejala seperti mengi, pembengkakan pada wajah atau lidah), pembentukan kelompok lepuh di atas kulit, masalah ginjal, impotensi, peningkatan keringat, kelebihan eosinofil (sejenis sel darah putih), ketidaknyamanan atau pembesaran payudara pada pria, kenaikan atau penurunan berat badan, takikardia, vaskulitis (radang pembuluh darah), reaksi fotosensitifitas (peningkatan sensitivitas kulit terhadap matahari), demam, penurunan, perubahan parameter laboratorium: kadar kalium darah tinggi yang reversibel pada penghentian, kadar natrium rendah, hipoglikemia (kadar gula darah sangat rendah) pada pasien diabetes, peningkatan ureum darah, dan peningkatan kreatinin darah.
- Efek samping yang jarang (dapat mempengaruhi hingga 1 dari 1000 orang): gagal ginjal akut; gejala kondisi yang disebut SIADH (sekresi hormon antidiuretik yang tidak tepat): urin berwarna gelap, merasa sakit (mual) atau sedang sakit (muntah), kram otot, kebingungan dan kejang; urin yang keluar menurun atau tidak ada; psoriasis memburuk; perubahan parameter laboratorium: peningkatan kadar enzim hati, kadar bilirubin serum yang tinggi.
- Efek samping yang sangat jarang (dapat mempengaruhi hingga 1 dari 10.000 orang): gangguan kardiovaskular (angina, serangan jantung dan stroke), pneumonia eosinofilik (jenis pneumonia yang jarang), pembengkakan kelopak mata, wajah atau bibir, pembengkakan lidah dan tenggorokan , yang menyebabkan kesulitan bernapas yang hebat, reaksi kulit yang parah termasuk ruam kulit yang intens, gatal-gatal, kemerahan pada kulit di seluruh tubuh Anda, gatal parah, lepuh, pengelupasan dan pembengkakan pada kulit, radang selaput lendir (Stevens Johnson Syndrome), eritema multiforme (ruam kulit yang sering dimulai dengan bercak merah gatal di wajah, lengan atau kaki), kepekaan terhadap cahaya, perubahan nilai darah seperti jumlah sel darah putih dan merah yang lebih rendah, hemoglobin yang lebih rendah, jumlah trombosit darah yang lebih rendah, gangguan darah, radang pankreas yang dapat menyebabkan sakit perut dan punggung yang parah disertai dengan perasaan tidak enak badan, fungsi hati yang tidak normal, radang hati (hepatitis), kulit menguning (jaundice), peningkatan enzim hati yang mungkin berpengaruh pada beberapa tes medis, perut kembung (gastritis), gangguan saraf yang dapat menyebabkan kelemahan, kesemutan atau mati rasa, peningkatan ketegangan otot, pembengkakan gusi, kelebihan gula dalam darah (hiperglikemia),

- Frekuensi tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia): gemetar, postur kaku, wajah seperti topeng, gerakan lambat dan terseret, berjalan tidak seimbang, perubahan warna, mati rasa dan nyeri pada jari tangan atau kaki (fenomena Raynaud).

Jika Anda memiliki gejala-gejala ini, hubungi dokter Anda sesegera mungkin.

Pelaporan efek samping

Jika Anda mengalami efek samping, konsultasikan kepada dokter atau apoteker atau perawat Anda, termasuk efek samping yang belum tercantum dalam leaflet ini.
Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lengkap mengenai keamanan obat ini.

5. Bagaimana cara menyimpan Coveram

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan menggunakan obat ini setelah tanggal kadaluwarsa yang tertera pada dus dan pada botol. Tanggal kadaluwarsa mengacu pada hari terakhir dari bulan itu.
Tutup botol dengan rapat untuk melindungi dari kelembapan. Simpan dalam kemasan aslinya. Produk obat ini tidak memerlukan kondisi penyimpanan suhu khusus.

Jangan membuang obat-obatan apapun melalui air limbah atau sampah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat-obatan yang sudah tidak lagi Anda digunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi paket dan informasi lainnya

Apakah yang terkandung dalam Coveram

Zat aktifnya adalah perindopril arginine dan amlodipine.
Coveram 5mg / 5mg: satu tablet mengandung 5 mg perindopril arginine dan 5 mg amlodipine.
Coveram 10mg / 5mg: satu tablet mengandung 10 mg perindopril arginine dan 5 mg amlodipine.
Coveram 5mg / 10mg: satu tablet mengandung 5 mg perindopril arginine dan 10 mg amlodipine.
Coveram 10mg / 10mg: satu tablet mengandung 10 mg perindopril arginine dan 10 mg amlodipine.

Seperti apa tampilan dan isi Coveram pada kemasan

Coveram 5mg / 5mg tablets berwarna putih, tablet berbentuk batang, panjang tablet 8.5 mm dan lebar 4.5 mm, dengan tanda 5/5 pada salah satu permukaan dan pada permukaan lainnya.
Coveram 10mg / 5mg tablets berwarna putih, tablet berbentuk segitiga, 9.5 mm × 8.8 mm × 8.8 mm, dengan tanda 10/5 pada salah satu permukaan dan pada permukaan lainnya.
Coveram 5mg / 10mg tablets berwarna putih, tablet berbentuk persegi panjang, panjang 8 mm dan lebar 8 mm, dengan tanda 5/10 pada salah satu permukaan dan pada permukaan lainnya.
Coveram 10mg / 10mg tablets berwarna putih, tablet berbentuk bundar, diameter 8.5 mm, dengan tanda 10/10 pada salah satu permukaan dan pada permukaan lainnya.

Dus, 1 botol plastik berisi 30 tablet.

COVERAM 5 mg / 5 mg Reg. No. : DKI1631600710A1

COVERAM 5 mg / 10 mg Reg. No. : DKI1631600710C1

COVERAM 10 mg / 5 mg Reg. No. : DKI1631600710B1

COVERAM 10 mg / 10 mg Reg. No. : DKI1631600710D1

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