4.2 Posology and method of administration

Oral route.
One tablet per day as a single dose, preferably to be taken in the morning and before a meal.
The fixed dose combination is not suitable for initial therapy.
If a change of posology is required, the dose of COVERAM could be modified or individual titration with free combination may be considered.

Special populations

Patients with renal impairment and elderly (see sections 4.4 and 5.2)
Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.
COVERAM can be administered in patients with Clcr ≥60 ml/min, and is not suitable for patients with Clcr <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 dialysable.

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

**Paediatric populations**

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.

### 4.3 Contraindications

**Linked to perindopril:**
- Hypersensitivity to perindopril or to any other ACE inhibitor,
- History of angioedema associated with previous ACE inhibitor therapy,
- Hereditary or idiopathic angioedema,
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6),
- 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 4.5 and 5.1).

**Linked to amlodipine:**
- Severe hypotension,
- Hypersensitivity to amlodipine 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.

### 4.4 Special warnings and precautions for use

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

**Linked to perindopril**

**Special warnings**

Hypersensitivity/Angioedema:
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, COVERAM should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8).

**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/Apaemia: 
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).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS): 
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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 4.3 and 4.6).

Precautions for use

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

Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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

Renal impairment: 
In cases of renal impairment (creatinine clearance <60 ml/min) an individual dose titration with the monocomponents is recommended (see section 4.2).
Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8).

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with 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 4.8).

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.

Hyperkalemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of perindopril and any of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

Linked to amlodipine:

Precautions for use
The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Use in patients with cardiac failure:
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with
severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

*Use in patients with impaired hepatic function:* The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

*Use in elderly patients:* In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

*Use in 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 Lapp lactase deficiency should not take this medicinal product.

**Interactions**

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

**4.5 Interaction with other medicinal products and other forms of interaction**

**Linked to perindopril**

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

**Concomitant use not recommended:**

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

**Lithium:**

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

**Estramustine:**

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

**Concomitant use which requires special care:**

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

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

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

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

**Sympathomimetics:**
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

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

**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: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

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.

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**Diuretics:**
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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 5.3).

Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Linked to amlodipine

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

In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Lactation:

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

It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility:

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

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

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

| Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/1000); rare (≥1/10000 to <1/10000); not known (cannot be estimated from the available data). |

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucopenia/neutropenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Agranulocytosis or pancytopenia (see section 4.4)</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Thrombocytopenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Decrease in haemoglobin and haematocrit</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>Very rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td>Hypoglycaemia (see sections 4.4 and 4.5)</td>
<td>-</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Mood changes (including anxiety)</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Depression</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Confusion</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

| Nervous System disorders | | |
|--------------------------|-------------------|
| Somnolence (especially at the beginning of the treatment) | Common |
| Dizziness (especially at the beginning of the treatment) | Common |
| Headache (especially at the beginning of the treatment) | Common |
| Dysesthesia | Uncommon |
| Tremor | Uncommon |
| Hypoesthesia | Uncommon |
| Paresthesia | Uncommon |
| Syncope | Very rare |
| Hypertonia | Not known |
| Peripheral neuropathy | Very rare |
| Vertigo | Common |

| Eye Disorders | | |
|----------------|-----------------|
| Visual disturbances (including diplopia) | Uncommon |
| | Common |

| Ear and labyrinth disorders | | |
|-----------------------------|-------------------|
| Tinnitus | Uncommon |
| | Common |

| Cardiac Disorders | | |
|-------------------|-------------------|
| Palpitations | Common |
| Angina pectoris | - |
| Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4) | Very rare |
| Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) | Very rare |

| Vascular Disorders | | |
|-------------------|-------------------|
| Flushing | Common |
| Hypotension (and effects related to hypotension) | Very rare |
| Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4) | Very rare |
| Vasculitis | Not known |

| Respiratory, Thoracic and Mediastinal Disorders | | |
|-----------------|-------------------|
| Rhinitis | Uncommon |
| Cough | Very rare |
| Bronchospasm | - |
| Eosinophilic pneumonia | Uncommon |

| Gastro-intestinal Disorders | | |
|-----------------------------|-------------------|
| Gingival hyperplasia | Very rare |
| Abdominal pain, nausea | Common |
| Vomiting | Common |
| Dyspepsia | Common |
| Altered bowel habits | Common |
| Dry mouth | Common |
| Diarrhoea, constipation | Very rare |
| Pancreatitis | Very rare |
| Gastritis | Common |

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4.9 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.

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

Additional information linked to amlodipine

Exceptional cases of extrapyramidal syndrome have been reported.
5. PHARMACOLOGICAL PROPERTIES

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

Perindopril:
Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

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

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 with-
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).

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 1 mm 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.

**Patients with coronary artery disease (CAD):**

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-center, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitaliza-
apies 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).

5.2 Pharmacokinetic properties
The rate and extent of absorption of perindopril and amlodipine from COVERAM are not significantly different, respectively, from the rate and extent of absorption of perindopril and amlodipine from COVERAM. See Table 1.

Use in patients with heart failure:
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology. A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined morbidity and morbidity with heart failure.

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

Treatment to prevent heart attack trial (ALLHAT):
A randomized double-blind morbidity-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%).

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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Amlodipine</th>
<th>Placebo</th>
<th>Enalapril</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse cardiovascular events</td>
<td>110 (16.6)</td>
<td>151 (23.1)</td>
<td>136 (20.2)</td>
<td>0.69 (0.54-0.88)</td>
<td>0.003</td>
</tr>
<tr>
<td>Individual Components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>78 (11.8)</td>
<td>103 (15.7)</td>
<td>95 (14.1)</td>
<td>0.73 (0.54-0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>51 (7.7)</td>
<td>84 (12.8)</td>
<td>86 (12.8)</td>
<td>0.58 (0.41-0.82)</td>
<td>0.002</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>14 (2.1)</td>
<td>19 (2.9)</td>
<td>11 (1.6)</td>
<td>0.73 (0.37-1.46)</td>
<td>0.37</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>6 (0.9)</td>
<td>12 (1.8)</td>
<td>8 (1.2)</td>
<td>0.50 (0.19-1.32)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>5 (0.8)</td>
<td>2 (0.3)</td>
<td>5 (0.7)</td>
<td>2.46 (0.48-12.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>3 (0.5)</td>
<td>5 (0.8)</td>
<td>4 (0.6)</td>
<td>0.59 (0.14-2.47)</td>
<td>0.46</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>0</td>
<td>4 (0.6)</td>
<td>1 (0.1)</td>
<td>NA</td>
<td>0.04</td>
</tr>
<tr>
<td>New-onset peripheral vascular disease</td>
<td>5 (0.8)</td>
<td>2 (0.3)</td>
<td>8 (1.2)</td>
<td>2.6 (0.50-13.4)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

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

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.

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

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

5.3 Preclinical safety data

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

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

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

**Amlodipine:**

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 besylate 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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470B)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Keep the container tightly closed in order to protect from moisture. Store in the original package.

6.5 Nature and contents of container
5, 7, 10, 14, 20, 28, 30 or 50 tablets in polypropylene container equipped with a low density polyethylene flow reducer and a low density polyethylene stopper containing a desiccant gel.
Box of 1 container of 5, 7, 10, 14, 20, 28, 30 or 50 tablets.
Box of 2 containers of 28, 30 or 50 tablets.
Box of 3 containers of 30 tablets.
Box of 4 containers of 30 tablets.
Box of 10 containers of 50 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes Cedex
France

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