Public Assessment Report

Decentralised Procedure

PERINDOPRIL/AMLODIPINE 4 MG/5 MG TABLETS
PERINDOPRIL/AMLODIPINE 4 MG/10 MG TABLETS
PERINDOPRIL/AMLODIPINE 8 MG/5 MG TABLETS
PERINDOPRIL/AMLODIPINE 8 MG/10 MG TABLETS

(Perindopril tert-butyamine and amlodipine besilate)

Procedure No: UK/H/4348 & 4620-1/001-4/DC

UK Licence No: PL 01656/0114-7 & 0133-40.

KRKA D.D.
LAY SUMMARY

On 22 June 2011, Czech Republic, Spain, France, Hungary, Italy, Lithuania, Latvia, the Netherlands, Poland, Portugal, Romania, Slovenia, Slovakia and the UK agreed to grant Marketing Authorisations to KRKA d.d for the medicinal products Perindopril/Amlodipine 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets (PL 01656/0114-7 & 0133-40; UK/H/4348 & 4620-1/001-4/DC). These were Decentralised Procedures (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, product licences were granted in the UK on 22 July 2011.

These are prescription-only medicines (POM) for the treatment of high blood pressure (hypertension) and/or stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked).

Perindopril/Amlodipine tablets are a combination of two active ingredients, perindopril and amlodipine. Perindopril is an angiotensin converting enzyme (ACE) inhibitor. Amlodipine is a calcium antagonist, which belongs to a class of medicines called dihydropyridines. Together they work to widen and relax the blood vessels, which results in a reduction of blood pressure. Blood can flow through the body more easily and the heart does not need to work so hard.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Perindopril/Amlodipine 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets outweigh the risks.
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## Module 1

| **Product Name** | Perindopril/Amlodipine 4 mg/5 mg tablets  
| | Perindopril/Amlodipine 4 mg/10 mg tablets  
| | Perindopril/Amlodipine 8 mg/5 mg tablets  
| | Perindopril/Amlodipine 8 mg/10 mg tablets  |
| **Type of Application** | Fixed combination, Article 10(b) |
| **Active Substances** | Perindopril tert-butylamine and amlodipine besilate |
| **Form** | Tablet |
| **Strength** | 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg |
| **MA Holder** | KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8000 Novo mesto, Slovenia |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | UK/H/4348/001-4/DC: Czech Republic, Spain, Hungary, Italy, Lithuania, Latvia, the Netherlands, Poland, Portugal, Romania, Slovenia and Slovakia.  
| | UK/H/4621/001-4/DC: Czech Republic, Hungary, Lithuania, Poland, Slovenia and Slovakia. |
| **Procedure Number** | UK/H/4348 & 4620-1/001-4/DC |
| **Timetable** | Day 210 – 22 June 2011 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Perindopril/Amlodipine 4 mg/5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 mg perindopril) and 5 mg amlodipine (as besilate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

White to almost white, round, slightly biconvex tablets with bevelled edges.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Perindopril/Amlodipine is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

4.2 Posology and method of administration
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 the change of the dosage is needed, it should be carried out by individual titration of the free combination’s ingredients.

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.

Perindopril/Amlodipine 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.

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Patients with hepatic impairment: see sections 4.4 and 5.2
A dosage regimen for patients with hepatic impairment has not been established. Therefore, Perindopril/Amlodipine should be administered with caution.

Paediatric population
Perindopril/Amlodipine should not be used in children and adolescents as the efficacy and tolerability of perindopril alone or in combination with amlodipine, 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).

Linked to amlodipine
- Severe hypotension,
- Hypersensitivity to amlodipine or to any other dihydropyridines,
- Shock, including cardiogenic shock,
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis),
- Haemodynamically unstable heart failure after acute myocardial infarction.

**Linked to Perindopril/Amlodipine**

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

- Hypersensitivity to any of the excipients.

### 4.4 Special warnings and precautions for use

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

**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, Perindopril/Amlodipine 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/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).
Pregnancy:
ACE inhibitors should not be initiated during pregnancy. 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 (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 Perindopril/Amlodipine.

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 preexisting 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).

Ethnic differences:
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, Perindopril/Amlodipine 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. Risk factors for the development of hyperkalaemia 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. Hyperkalaemia 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

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

Patients with heart failure:
Patients with cardiac failure should be treated with caution.

In a long-term, placebo controlled study of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

Linked to Perindopril/Amlodipine

Precautions for use

Interactions
The concomitant use of Perindopril/Amlodipine with lithium, potassium-sparing diuretics or potassium supplements is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Linked to perindopril

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 drugs (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.

**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 which requires special care:**

**CYP3A4 inhibitors:**
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of amlodipine increased by 22% and 50% respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

**CYP3A4 inducers (rifampicin, Hypericum perforatum, anticonvulsant agents i.e carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone):**
The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine due to an increase of the hepatic metabolism of amlodipine by these inducers. Amlodipine should be used with caution together with CYP3A4 inducers and posology of amlodipine could be adapted if needed.
**Concomitant use to be taken into consideration:**
Beta-blockers used in heart failure (bisoprolol, carvedilol, metoprolol):
Risk of hypotension, heart weakness in patients with cardiac heart failure, be it latent or uncontrolled (addition of negative inotropic effect). Furthermore, the beta-blocker may minimize the sympathetic reflex in case of excessive heamodynamic repercussion.

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

Indeed, specific studies conducted with some drugs have shown no influence on amlodipine:
- Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.
- when sildenafil and amlodipine were used in combination, each one independently exerted its own blood pressure lowering effect.
- grapefruit juice: co-administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Moreover, specific studies conducted with some drugs have shown that amlodipine has no influence on their pharmacokinetics parameters:
- atorvastatin: co-administration of multiple doses of 10 mg amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetics parameters of atorvastatin.
- digoxin: co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
- warfarin: in heathy male volunteers, the co-administration of amlodipine with warfarin did not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.
- ciclosporin: Pharmacokinetic studies with ciclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

**Concomitant use which requires special care:**
Baclofen. Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adjustment of the antihypertensive if necessary.

**Concomitant use to be taken into consideration:**
- Antihypertensive agents (such as beta-blockers) and vasodilators:
- Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine.
- Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.
- Corticosteroids, tetracosactide: reduction in antihypertensive effect (salt and water retention due to corticosteroids).
- Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin): increased antihypertensive effect and increased risk of orthostatic hypotension.
- Amifostine: may potentiate the antihypertensive effect of amlodipine.
- Tricyclic antidepressants/antipsychotics/anaesthetics: increased antihypertensive effect and increased risk of orthostatic hypotension.

### 4.6 Fertility, Pregnancy and lactation
Given the effects of the individual components in this combination product on pregnancy and lactation:

Perindopril/Amlodipine is not recommended during the first trimester of pregnancy.
Perindopril/Amlodipine is contraindicated during the second and third trimesters of pregnancy.

Perindopril/Amlodipine is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Perindopril/Amlodipine taking into account the importance of this therapy for the mother.
Pregnancy:
Linked to perindopril
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, 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.

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

Lactation:
Linked to perindopril
Because no information is available regarding the use of perindopril during breastfeeding, Perindopril/Amlodipine 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. Similar calcium channel blockers of the dihydropyridine type are 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:
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 Perindopril/Amlodipine on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

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 (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
<th>Frequency</th>
<th>Amlodipine</th>
<th>Perindopril</th>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td>Leucopenia/neutropenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
<td></td>
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<tr>
<td></td>
<td>Agranulocytosis or pancytopenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
<td></td>
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<tr>
<td></td>
<td>Thrombocytopenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
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<tr>
<td></td>
<td>Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)</td>
<td>-</td>
<td>Very rare</td>
<td></td>
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<tr>
<td></td>
<td>Decrease in haemoglobin and haematocrit</td>
<td>-</td>
<td>Very rare</td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td>Allergic reaction: Urticaria</td>
<td>Very rare</td>
<td>Uncommon</td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia</td>
<td>Very rare</td>
<td>-</td>
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<tr>
<td></td>
<td>Weight gain</td>
<td>Uncommon</td>
<td>-</td>
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<td></td>
<td>Weight decrease</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
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<tr>
<td></td>
<td>Hypoglycaemia (see sections 4.4 and 4.5)</td>
<td>-</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
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<td></td>
<td>Mood changes</td>
<td>Uncommon</td>
<td>Uncommon</td>
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<td></td>
<td>Sleep disturbances</td>
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<td>Uncommon</td>
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<td>Nervous system disorders</td>
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<td></td>
<td>Dizziness</td>
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<td></td>
<td>Headache</td>
<td>Common</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypoesthesia, Paresthesia</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertonia</td>
<td>Very rare</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Very rare</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
<td>-</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>-</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbances</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Tinnitus</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>Common</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angina pain</td>
<td>Rare</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angina pectoris</td>
<td>-</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)</td>
<td>Very rare</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
<td>Common</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension (and effects related to hypotension)</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)</td>
<td>-</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
<td>Very rare</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>Uncommon</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>Very rare</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchospasm</td>
<td>-</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eosinophilic pneumonia</td>
<td>-</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gingival hyperplasia</td>
<td>Very rare</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain, nausea</td>
<td>Common</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
</tbody>
</table>
### MedDRA System Organ Class

<table>
<thead>
<tr>
<th>Undesirable Effects</th>
<th>Frequency</th>
<th>Amlodipine</th>
<th>Perindopril</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Altered bowel habits</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Dry mouth</strong></td>
<td>Uncommon</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Dysgeusia</strong></td>
<td>-</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td><strong>Taste perversion</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Diarrhoea, constipation</strong></td>
<td>-</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>Very rare</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td><strong>Gastritis</strong></td>
<td>Very rare</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis, cholestatic jaundice</strong></td>
<td>Very rare</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hepatitis either cytolytic or cholestatic (see section 4.4)</strong></td>
<td>-</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quincke’s oedema</strong></td>
<td>Very rare</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)</strong></td>
<td>-</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Erythema multiform</strong></td>
<td>Very rare</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td><strong>Alopecia</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Purpura</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Skin discoloration</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Increased sweating</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sweating</strong></td>
<td>-</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td><strong>Stevens-Johnson Syndrome</strong></td>
<td>Very rare</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arthralgia, myalgia</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Muscle cramps</strong></td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td><strong>Back pain</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Micturition disorder, nocturia, increased urinary frequency</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Renal impairment</strong></td>
<td>-</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Acute renal failure</strong></td>
<td>-</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Impotence</strong></td>
<td>Uncommon</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Gynaecomastia</strong></td>
<td>Uncommon</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oedema, peripheral oedema</strong></td>
<td>Common</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>Common</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Chest pain</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Malaise</strong></td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis)</strong></td>
<td>Very rare</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Serum bilirubin and liver enzymes elevation</strong></td>
<td>-</td>
<td>Rare</td>
<td>-</td>
</tr>
<tr>
<td><strong>Increases in blood urea and serum creatinine, hyperkalaemia (see section 4.4)</strong></td>
<td>-</td>
<td>Not known</td>
<td>-</td>
</tr>
</tbody>
</table>

Additional information linked to amlodipine
Exceptional cases of extrapyramidal syndrome have been reported with calcium channel blockers.

### 4.9 Overdose

There is no information on overdose with Perindopril/Amlodipine in humans.

For amlodipine, experience with intentional overdose in humans is limited. Large overdosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Any hypotension due to amlodipine overdosage calls for a monitoring in cardiologic intensive care unit. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Amlodipine is not dialyzable.
For perindopril, limited data are available for overdose in humans. Symptoms associated with the overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, 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 vitro.

Hypertension:

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100% of peak effects.

The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries.

Patients with stable coronary artery disease:

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

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 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.

Amlodipine

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully understood but is determined by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilation increases the supply in oxygen to myocardium in patients with Prinzmetal’s angina attack.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) throughout the 24 hour interval.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression. Amlodipine 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.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug (amlodipine or ACE-inhibitor as first-line) therapies to that of the thiazide diuretic, in mild to moderate hypertension. There were no significant difference in cardiovascular outcomes between amlodipine-based therapy and thiazide diuretic-based therapy.

Paediatric population

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2 Pharmacokinetic properties

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

Perindopril

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 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.

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. 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.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure (see section 4.2). Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

Amlodipine

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

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites. About 60% of the administered dose is excreted in the urine, 10% as unchanged amlodipine.

Use in the elderly: the time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. The recommended dosage regimen for the elderly is the same, although increasing the dose should take place with caution.

Use in patients with renal failure: see section 4.2.

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

Paediatric population

A population PK study has been conducted in 74 hypertensive children aged from 12 months to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/h respectively in males and 16.4 and 21.3 L/h respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

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
Carcinogenesis, Mutagenesis, Impairment of Fertility
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.

Reproductive studies have shown that calcium antagonists induce embryotoxic and/or teratogenic effects in several species, mainly as distal skeletal malformations.

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.

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.

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium hydrogen carbonate
Cellulose, microcrystalline (E460)
Maize starch, pregelatinised
Sodium starch glycolate (type A)
Silica, colloidal anhydrous
Magnesium stearate (E572)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container
Blister (OPA/Al/PVC//Al foil): 5, 7, 10, 14, 20, 28, 30, 50, 60, 90 and 100 tablets, in a carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8000 Novo mesto, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 01656/0114
PL 01656/0133
PL 01656/0137

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/07/2011

10 DATE OF REVISION OF THE TEXT
22/07/2011
NAME OF THE MEDICINAL PRODUCT
Perindopril/Amlodipine 4 mg/10 mg tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 mg perindopril) and 10 mg amlodipine (as besilate).
For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Tablet.
4 mg/10 mg: White to almost white, capsule shaped, biconvex tablets scored on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

CLINICAL PARTICULARS

4.1 Therapeutic indications
Perindopril/Amlodipine is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

4.2 Posology and method of administration
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 the change of the dosage is needed, it should be carried out by individual titration of the free combination’s ingredients.

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.
Perindopril/Amlodipine can be administered in patients with CrCl ≥ 60 ml/min, and is not suitable for patients with CrCl < 60 ml/min. In these patients, an individual dose titration with the monocomponents is recommended.
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Patients with hepatic impairment: see sections 4.4 and 5.2
A dosage regimen for patients with hepatic impairment has not been established. Therefore, Perindopril/Amlodipine should be administered with caution.

Paediatric population
Perindopril/Amlodipine should not be used in children and adolescents as the efficacy and tolerability of perindopril alone or in combination with amlodipine, 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).

Linked to amlodipine
- Severe hypotension,
- Hypersensitivity to amlodipine or to any other dihydropyridines,
- Shock, including cardiogenic shock,
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis),
- Haemodynamically unstable heart failure after acute myocardial infarction.

Linked to Perindopril/Amlodipine
All contraindications related to each monocomponent, as listed above, should apply also to the fixed combination of Perindopril/Amlodipine.
• Hypersensitivity to any of the excipients.

4.4 Special warnings and precautions for use

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

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, Perindopril/Amlodipine 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/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).

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. 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 (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 Perindopril/Amlodipine.

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 preexisting 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).

Ethnic differences:
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, Perindopril/Amlodipine 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. Risk factors for the development of hyperkalaemia 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. Hyperkalaemia 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**

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

Patients with heart failure:
Patients with cardiac failure should be treated with caution.
In a long-term, placebo controlled study of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

Linked to Perindopril/Amlodipine

**Precautions for use**

**Interactions**
The concomitant use of Perindopril/Amlodipine with lithium, potassium-sparing diuretics or potassium supplements is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

**Linked to perindopril**

**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 drugs (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.

**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 which requires special care:**

**CYP3A4 inhibitors:**
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of amlodipine increased by 22% and 50% respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

**CYP3A4 inducers (rifampicin, Hypericum perforatum, anticonvulsant agents i.e carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone):**
The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine due to an increase of the hepatic metabolism of amlodipine by these inducers. Amlodipine should be used with caution together with CYP3A4 inducers and posology of amlodipine could be adapted if needed.

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

Indeed, specific studies conducted with some drugs have shown no influence on amlodipine:
- Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.
• when sildenafil and amlodipine were used in combination, each one independently exerted its own blood pressure lowering effect.

• grapefruit juice: co-administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

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

• atorvastatin: co-administration of multiple doses of 10 mg amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetics parameters of atorvastatin.

• digoxin: co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

• warfarin: in healthy male volunteers, the co-administration of amlodipine did not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

• ciclosporin: Pharmacokinetic studies with ciclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

**Concomitant use which requires special care:**

Baclofen. Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adjustment of the antihypertensive if necessary.

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

- Antihypertensive agents (such as beta-blockers) and vasodilators:
- Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine.
- Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.
- Corticosteroids, tetracosactide: reduction in antihypertensive effect (salt and water retention due to corticosteroids).
- Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin): increased antihypertensive effect and increased risk of orthostatic hypotension.
- Amifostine: may potentiate the antihypertensive effect of amlodipine.
- Tricyclic antidepressants/antipsychotics/anaesthetics: increased antihypertensive effect and increased risk of orthostatic hypotension.

**4.6 Fertility, Pregnancy and lactation**

Given the effects of the individual components in this combination product on pregnancy and lactation: Perindopril/Amlodipine is not recommended during the first trimester of pregnancy. Perindopril/Amlodipine is contraindicated during the second and third trimesters of pregnancy. Perindopril/Amlodipine is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Perindopril/Amlodipine taking into account the importance of this therapy for the mother.

**Pregnancy:**

Linked to perindopril

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, 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. Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery. 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 fetus.

Lactation:

Linked to perindopril
Because no information is available regarding the use of perindopril during breastfeeding, Perindopril/Amlodipine 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. Similar calcium channel blockers of the dihydropyridine type are 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:
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 Perindopril/Amlodipine on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

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 (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
<th>Frequency Amlodipine</th>
<th>Perindopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Leucopenia/neutropenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Agranulocytosis or pancytopenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<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></td>
<td>Decrease in haemoglobin and haematocrit</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic reaction: Urticaria</td>
<td>Very rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Weight decrease</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia (see sections 4.4 and 4.5)</td>
<td>-</td>
<td>Not known</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mood changes</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Somnolence</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hypoesthesia, Paresthesia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypertonia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbances</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Tinnitus</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Angina pain</td>
<td>Rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Angina pectoris</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hypotension (and effects related to hypotension)</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
<td>Very rare</td>
<td>Not known</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>Uncommon</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>Very rare</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic pneumonia</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gingival hyperplasia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain, nausea</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Altered bowel habits</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Taste perversion</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>MedDRA System Organ Class</td>
<td>Undesirable Effects</td>
<td>Frequency</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Undesirable Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea, constipation</td>
<td></td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Gastritis</td>
<td></td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis, cholestatic jaundice</td>
<td></td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td>Hepatitis either cytolytic or cholestatic (see section 4.4)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quincke’s oedema</td>
<td></td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td>Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)</td>
<td>Very rare</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Erythema multiform</td>
<td></td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Purpura</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Increased sweating</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Stevens-Johnson Syndrome</td>
<td></td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia, myalgia</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micturition disorder, nocturia, increased urinary frequency</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Renal impairment</td>
<td></td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td></td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impotence</td>
<td></td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oedema, peripheral oedema</td>
<td></td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Malaise</td>
<td></td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis)</td>
<td>Very rare</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serum bilirubin and liver enzymes elevation</td>
<td></td>
<td>-</td>
<td>Rare</td>
</tr>
<tr>
<td>Increases in blood urea and serum creatinine, hyperkalaemia (see section 4.4)</td>
<td>-</td>
<td>Not known</td>
<td>-</td>
</tr>
</tbody>
</table>

Additional information linked to amlodipine
Exceptional cases of extrapyramidal syndrome have been reported with calcium channel blockers.

**4.9 Overdose**

There is no information on overdose with Perindopril/Amlodipine in humans.

For amlodipine, experience with intentional overdose in humans is limited. Large overdosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Any hypotension due to amlodipine overdosage calls for a monitoring in cardiologic intensive care unit. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Amlodipine is not dialyzable.

For perindopril, limited data are available for overdose in humans. Symptoms associated with the overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.
The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril can be removed from the systemic circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for treatment-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, 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 vitro.

Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100% of peak effects.

The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries.

Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 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.

Amlodipine
Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully understood but is determined by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilation increases the supply in oxygen to myocardium in patients with Prinzmetal’s angina attack.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) throughout the 24 hour interval.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression. Amlodipine 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.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug (amlodipine or ACE-inhibitor as first-line) therapies to that of the thiazide diuretic, in mild to moderate hypertension. There were no significant difference in cardiovascular outcomes between amlodipine-based therapy and thiazide diuretic-based therapy.

Paediatric population
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2 Pharmacokinetic properties
The rate and extent of absorption of perindopril and amlodipine from Perindopril/Amlodipine are not significantly different, respectively, from the rate and extent of absorption of perindopril and amlodipine from individual tablet formulations.

Perindopril
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 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.
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. 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.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure (see section 4.2). Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.

Dialysis clearance of perindoprilat is equal to 70 ml/min. Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

**Amlodipine**

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

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites. About 60% of the administered dose is excreted in the urine, 10% as unchanged amlodipine.

Use in the elderly: the time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. The recommended dosage regimen for the elderly is the same, although increasing the dose should take place with caution.

Use in patients with renal failure: see section 4.2.

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

**Paediatric population**

A population PK study has been conducted in 74 hypertensive children aged from 12 months to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/h respectively in males and 16.4 and 21.3 L/h respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

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**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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.

Reproductive studies have shown that calcium antagonists induce embryotoxic and/or teratogenic effects in several species, mainly as distal skeletal malformations.

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.

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.

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium hydrogen carbonate
Cellulose, microcrystalline (E460)
Maize starch, pregelatinised
Sodium starch glycolate (type A)
Silica, colloidal anhydrous
Magnesium stearate (E572)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container
Blister (OPA/Al/PVC/Al foil): 5, 7, 10, 14, 20, 28, 30, 50, 60, 90 and 100 tablets, in a carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8000 Novo mesto, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 01658/0115
PL 01656/0134
PL 01656/0138

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/07/2011

10 DATE OF REVISION OF THE TEXT
22/07/2011
1 NAME OF THE MEDICINAL PRODUCT
Perindopril/Amlodipine 8 mg/5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 5 mg amlodipine (as besilate).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
8 mg/5 mg: White to almost white, round, biconvex tablets with bevelled edges.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Perindopril/Amlodipine is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

4.2 Posology and method of administration
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 the change of the dosage is needed, it should be carried out by individual titration of the free combination’s ingredients.

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.
Perindopril/Amlodipine 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.
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Patients with hepatic impairment: see sections 4.4 and 5.2
A dosage regimen for patients with hepatic impairment has not been established. Therefore, Perindopril/Amlodipine should be administered with caution.

Paediatric population
Perindopril/Amlodipine should not be used in children and adolescents as the efficacy and tolerability of perindopril alone or in combination with amlodipine, 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).

Linked to amlodipine
- Severe hypotension,
- Hypersensitivity to amlodipine or to any other dihydropyridines,
- Shock, including cardiogenic shock,
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis),
- Haemodynamically unstable heart failure after acute myocardial infarction.

Linked to Perindopril/Amlodipine
All contraindications related to each monocomponent, as listed above, should apply also to the fixed combination of Perindopril/Amlodipine.
• Hypersensitivity to any of the excipients.

4.4 Special warnings and precautions for use

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

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, Perindopril/Amlodipine 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/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).

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. 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 (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 voleudepleted 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 Perindopril/Amlodipine.

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 preexisting 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).

Ethnic differences:
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, Perindopril/Amlodipine 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. Risk factors for the development of hyperkalaemia 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. Hyperkalaemia 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

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

Patients with heart failure:
Patients with cardiac failure should be treated with caution.
In a long-term, placebo controlled study of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

Linked to Perindopril/Amlodipine
Precautions for use

Interactions
The concomitant use of Perindopril/Amlodipine with lithium, potassium-sparing diuretics or potassium supplements is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Linked to perindopril

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 drugs (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.

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 which requires special care:
CYP3A4 inhibitors:
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of amlodipine increased by 22% and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

CYP3A4 inducers (rifampicin, Hypericum perforatum, anticonvulsant agents i.e carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone):
The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine due to an increase of the hepatic metabolism of amlodipine by these inducers. Amlodipine should be used with caution together with CYP3A4 inducers and posology of amlodipine could be adapted if needed.

Concomitant use to be taken into consideration:
Beta-blockers used in heart failure (bisoprolol, carvedilol, metoprolol):
Risk of hypotension, heart weakness in patients with cardiac heart failure, be it latent or uncontrolled (addition of negative inotropic effect). Furthermore, the beta-blocker may minimize the sympathetic reflex in case of excessive haemodynamic repercussion.

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

Indeed, specific studies conducted with some drugs have shown no influence on amlodipine:
• Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.
when sildenafil and amlodipine were used in combination, each one independently exerted its own blood pressure lowering effect.

grapefruit juice: co-administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

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

- atorvastatin: co-administration of multiple doses of 10 mg amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetics parameters of atorvastatin.
- digoxin: co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
- warfarin: in healthy male volunteers, the co-administration of amlodipine did not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.
- ciclosporin: Pharmacokinetic studies with ciclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

**Concomitant use which requires special care:**

Baclofen. Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adjustment of the antihypertensive if necessary.

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

- Antihypertensive agents (such as beta-blockers) and vasodilators:
- Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine.
- Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.
- Corticosteroids, tetracosactide: reduction in antihypertensive effect (salt and water retention due to corticosteroids).
- Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin): increased antihypertensive effect and increased risk of orthostatic hypotension.
- Amifostine: may potentiate the antihypertensive effect of amlodipine.
- Tricyclic antidepressants/antipsychotics/anaesthetics: increased antihypertensive effect and increased risk of orthostatic hypotension.

**4.6 Fertility, Pregnancy and lactation**

Given the effects of the individual components in this combination product on pregnancy and lactation:

Perindopril/Amlodipine is not recommended during the first trimester of pregnancy.

Perindopril/Amlodipine is contraindicated during the second and third trimesters of pregnancy.

Perindopril/Amlodipine is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Perindopril/Amlodipine taking into account the importance of this therapy for the mother.

**Pregnancy:**

Linked to perindopril

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, 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.

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

**Lactation:**

**Linked to perindopril**

Because no information is available regarding the use of perindopril during breastfeeding, Perindopril/Amlodipine 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. Similar calcium channel blockers of the dihydropyridine type are 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:**

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 Perindopril/Amlodipine on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

**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 (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
<th>Frequency Amlodipine</th>
<th>Perindopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Leucopenia/neutropenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Agranulocytosis or pancytopenia (see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<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></td>
<td>Decrease in haemoglobin and haematocrit</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>MedDRA System Organ Class</td>
<td>Undesirable Effects</td>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>Perindopril</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic reaction: Urticaria</td>
<td>Very rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Weight decrease</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Hypoglycaemia (see sections 4.4 and 4.5)</td>
<td>-</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mood changes</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Somnolence</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hypoesthæsia, Paresthæsia</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hypertonia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbances</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Tinnitus</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Angina pain</td>
<td>Rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Angina pectoris</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hypotension (and effects related to hypotension)</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
<td>Very rare</td>
<td>Not known</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>Uncommon</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>Very rare</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic pneumonia</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gingival hyperplasia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain, nausea</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Altered bowel habits</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Taste perversion</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea, constipation</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Gastritis</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatitis, cholestatic jaundice</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hepatitis either cytolytic or cholestatic (see section 4.4)</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Skin and subcutaneous</td>
<td>Quincke’s oedema</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td>MedDRA System Organ Class</td>
<td>Undesirable Effects</td>
<td>Frequency Amlodipine</td>
<td>Frequency Perindopril</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------</td>
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<td>----------------------</td>
</tr>
<tr>
<td>Tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)</td>
<td>-</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Erythema multiform</td>
<td>Very rare</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Purpura</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Increased sweating</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>-</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson Syndrome</td>
<td>Very rare</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia, myalgia</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micturition disorder, nocturia, increased urinary frequency</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td>-</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>-</td>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impotence</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oedema, peripheral oedema</td>
<td>Common</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Common</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>Uncommon</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>Uncommon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis)</td>
<td>Very rare</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin and liver enzymes elevation</td>
<td>-</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Increases in blood urea and serum creatinine, hyperkalaemia (see section 4.4)</td>
<td>-</td>
<td>Not known</td>
<td></td>
</tr>
</tbody>
</table>

Additional information linked to amlodipine

Exceptional cases of extrapyramidal syndrome have been reported with calcium channel blockers.

### 4.9 Overdose

There is no information on overdose with Perindopril/Amlodipine in humans.

For amlodipine, experience with intentional overdose in humans is limited. Large overdosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Any hypotension due to amlodipine overdosage calls for a monitoring in cardiologic intensive care unit. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Amlodipine is not dialyzable.

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

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

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, 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 vitro.

Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100% of peak effects.

The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries.

Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 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.
**Amlodipine**

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully understood but is determined by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilatation increases the supply in oxygen to myocardium in patients with Prinzmetal’s angina attack.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) throughout the 24 hour interval.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression. Amlodipine 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.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug (amlodipine or ACE-inhibitor as first-line) therapies to that of the thiazide diuretic, in mild to moderate hypertension. There were no significant difference in cardiovascular outcomes between amlodipine-based therapy and thiazide diuretic-based therapy.

**Paediatric population**

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

### 5.2 Pharmacokinetic properties

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

**Perindopril**

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 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.

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. 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.
Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure (see section 4.2). Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

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

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

Amlodipine is extensively metabolised by the liver to inactive metabolites. About 60% of the administered dose is excreted in the urine, 10% as unchanged amlodipine.

Use in the elderly: the time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. The recommended dosage regimen for the elderly is the same, although increasing the dose should take place with caution.

Use in patients with renal failure: see section 4.2.

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

Paediatric population
A population PK study has been conducted in 74 hypertensive children aged from 12 months to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/h respectively in males and 16.4 and 21.3 L/h respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

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
Carcinogenesis, Mutagenesis, Impairment of Fertility
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.
Reproductive studies have shown that calcium antagonists induce embryotoxic and/or teratogenic effects in several species, mainly as distal skeletal malformations.

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.

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.

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Sodium hydrogen carbonate
- Cellulose, microcrystalline (E460)
- Maize starch, pregelatinised
- Sodium starch glycolate (type A)
- Silica, colloidal anhydrous
- Magnesium stearate (E572)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container
Blister (OPA/Al/PVC//Al foil): 5, 7, 10, 14, 20, 28, 30, 50, 60, 90 and 100 tablets, in a carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8000 Novo mesto, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
- PL 01656/0116
- PL 01656/0135
- PL 01656/0139

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/07/2011

10 DATE OF REVISION OF THE TEXT
22/07/2011
1 **NAME OF THE MEDICINAL PRODUCT**
Perindopril/Amlodipine 8 mg/10 mg tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 10 mg amlodipine (as besilate)

For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Tablet.

8 mg/10 mg: White to almost white, round, biconvex tablets with bevelled edges and a score line on one side. The tablet can be divided into equal halves.

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
Perindopril/Amlodipine is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

4.2 **Posology and method of administration**
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 the change of the dosage is needed, it should be carried out by individual titration of the free combination’s ingredients.

*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.

Perindopril/Amlodipine can be administered in patients with Clcr $\geq 60$ 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.
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

*Patients with hepatic impairment: see sections 4.4 and 5.2*
A dosage regimen for patients with hepatic impairment has not been established. Therefore, Perindopril/Amlodipine should be administered with caution.

*Paediatric population*
Perindopril/Amlodipine should not be used in children and adolescents as the efficacy and tolerability of perindopril alone or in combination with amlodipine, 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).

**Linked to amlodipine**
- Severe hypotension,
- Hypersensitivity to amlodipine or to any other dihydropyridines,
- Shock, including cardiogenic shock,
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis),
- Haemodynamically unstable heart failure after acute myocardial infarction.

**Linked to Perindopril/Amlodipine**
4.4 Special warnings and precautions for use

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

Hypersensitivity to any of the excipients.

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, Perindopril/Amlodipine 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/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).

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. 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 (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 Perindopril/Amlodipine.

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 preexisting 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).

**Ethnic differences:**
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, Perindopril/Amlodipine 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. Risk factors for the development of hyperkalaemia 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. Hyperkalaemia 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**

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

**Patients with heart failure:**
Patients with cardiac failure should be treated with caution.
In a long-term, placebo controlled study of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

**Linked to Perindopril/Amlodipine**

**Precautions for use**

**Interactions**
The concomitant use of Perindopril/Amlodipine with lithium, potassium-sparing diuretics or potassium supplements is not recommended (see section 4.5).

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

**Linked to perindopril**

**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 drugs (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.

**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 which requires special care:**

**CYP3A4 inhibitors:**

With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of amlodipine increased by 22% and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

**CYP3A4 inducers (rifampicin, Hypericum perforatum, anticonvulsant agents i.e carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone):**

The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine due to an increase of the hepatic metabolism of amlodipine by these inducers. Amlodipine should be used with caution together with CYP3A4 inducers and posology of amlodipine could be adapted if needed.

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

Beta-blockers used in heart failure (bisoprolol, carvedilol, metoprolol):

Risk of hypotension, heart weakness in patients with cardiac heart failure, be it latent or uncontrolled (addition of negative inotropic effect). Furthermore, the beta-blocker may minimize the sympathetic reflex in case of excessive haemodynamic repercussion.

**Others combinations:**

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

Indeed, specific studies conducted with some drugs have shown no influence on amlodipine:

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

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

- atorvastatin: co-administration of multiple doses of 10 mg amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetics parameters of atorvastatin.
- digoxin: co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
- warfarin: in heathy male volunteers, the co-administration of amlodipine did not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.
- ciclosporin: Pharmacokinetic studies with ciclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

Concomitant use which requires special care:
Baclofen. Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adjustment of the antihypertensive if necessary.

Concomitant use to be taken into consideration:

- Antihypertensive agents (such as beta-blockers) and vasodilators.
- Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine.
- Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.
- Corticosteroids, tetracosactide: reduction in antihypertensive effect (salt and water retention due to corticosteroids).
- Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin): increased antihypertensive effect and increased risk of orthostatic hypotension.
- Amifostine: may potentiate the antihypertensive effect of amlodipine.
- Tricyclic antidepressants/antipsychotics/anaesthetics: increased antihypertensive effect and increased risk of orthostatic hypotension.

4.6 Fertility, Pregnancy and lactation
Given the effects of the individual components in this combination product on pregnancy and lactation: Perindopril/Amlodipine is not recommended during the first trimester of pregnancy. Perindopril/Amlodipine is contraindicated during the second and third trimesters of pregnancy.

Perindopril/Amlodipine is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Perindopril/Amlodipine taking into account the importance of this therapy for the mother.

Pregnancy:

Linked to perindopril
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established
safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, 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.
Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery. 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 fetus.

Lactation:

Linked to perindopril
Because no information is available regarding the use of perindopril during breastfeeding, Perindopril/Amlodipine 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. Similar calcium channel blockers of the dihydropyridine type are 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:

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 Perindopril/Amlodipine on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

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 (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
<th>Frequency Amlodipine</th>
<th>Frequency Perindopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Leucopenia/neutropenia (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Agranulocytosis or pancytopenia (see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MedDRA System Organ Class</td>
<td>Undesirable Effects</td>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>Perindopril</td>
</tr>
<tr>
<td>Undesirable Effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (see section 4.4)</td>
<td></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>
<td>-</td>
</tr>
<tr>
<td>Decrease in haemoglobin and haematocrit</td>
<td>-</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic reaction: Urticaria</td>
<td>Very rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperglycaemia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Weight decrease</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia (see sections 4.4 and 4.5)</td>
<td>-</td>
<td>Not known</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mood changes</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Somnolence</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hypoesthæsia, Paresthæsia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypertonia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbances</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Tinnitus</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Angina pain</td>
<td>Rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Angina pectoris</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hypotension (and effects related to hypotension)</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
<td>Very rare</td>
<td>Not known</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>Uncommon</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>Very rare</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic pneumonia</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gingival hyperplasia</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain, nausea</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Altered bowel habits</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Taste perversion</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea, constipation</td>
<td>-</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Gastritis</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td>MedDRA System Organ Class</td>
<td>Undesirable Effects</td>
<td>Frequency Amlodipine</td>
<td>Perindopril</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatitis, cholestatic jaundice</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hepatitis either cytolitic or cholestatic (see section 4.4)</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Quincke’s oedema</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Erythema multiform</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Purpura</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Skin discoloration</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Increased sweating</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sweating</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Stevens-Johnson Syndrome</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, myalgia</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Muscle cramps</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Micturition disorder, nocturia, increased urinary frequency</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Renal impairment</td>
<td>-</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Acute renal failure</td>
<td>-</td>
<td>Very rare</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Impotence</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Gynaecomastia</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Oedema, peripheral oedema</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
<td>Uncommon</td>
<td>-</td>
</tr>
<tr>
<td>Investigations</td>
<td>Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis)</td>
<td>Very rare</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Serum bilirubin and liver enzymes elevation</td>
<td>-</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Increases in blood urea and serum creatinine, hyperkalaemia (see section 4.4)</td>
<td>-</td>
<td>Not known</td>
</tr>
</tbody>
</table>

Additional information linked to amlodipine
Exceptional cases of extrapyramidal syndrome have been reported with calcium channel blockers.

4.9 Overdose
There is no information on overdose with Perindopril/Amlodipine in humans.

For amlodipine, experience with intentional overdose in humans is limited. Large overdosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Any hypotension due to amlodipine overdose calls for a monitoring in cardiology intensive care unit. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Amlodipine is not dialyzable.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, 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 vitro.

Hypertension:

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.

The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100% of peak effects.

The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries.

Patients with stable coronary artery disease:

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

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 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.

**Amlodipine**

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully understood but is determined by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilation increases the supply in oxygen to myocardium in patients with Prinzmetal’s angina attack.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) throughout the 24 hour interval.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression. Amlodipine 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.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug (amlodipine or ACE-inhibitor as first-line) therapies to that of the thiazide diuretic, in mild to moderate hypertension. There were no significant difference in cardiovascular outcomes between amlodipine-based therapy and thiazide diuretic-based therapy.

**Paediatric population**

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

### 5.2 Pharmacokinetic properties

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

**Perindopril**

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 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.
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. 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.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure (see section 4.2). Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

**Amlodipine**

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

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

Amlodipine is extensively metabolised by the liver to inactive metabolites. About 60% of the administered dose is excreted in the urine, 10% as unchanged amlodipine.

Use in the elderly: the time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. The recommended dosage regimen for the elderly is the same, although increasing the dose should take place with caution.

Use in patients with renal failure: see section 4.2.

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

**Paediatric population**

A population PK study has been conducted in 74 hypertensive children aged from 12 months to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/h respectively in males and 16.4 and 21.3 L/h respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

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**

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

Reproductive studies have shown that calcium antagonists induce embryotoxic and/or teratogenic effects in several species, mainly as distal skeletal malformations.

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.

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.

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium hydrogen carbonate
Cellulose, microcrystalline (E460)
Maize starch, pregelatinised
Sodium starch glycolate (type A)
Silica, colloidal anhydrous
Magnesium stearate (E572)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container
Blister (OPA/Al/PVC//Al foil): 5, 7, 10, 14, 20, 28, 30, 50, 60, 90 and 100 tablets, in a carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8000 Novo mesto, Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 01656/0117
PL 01656/0136
PL 01656/0140

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/07/2011

10 DATE OF REVISION OF THE TEXT
22/07/2011
Module 3

The following text is the approved Patient Information Leaflet (PIL) text. No PIL mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-ups has been obtained.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Perindopril/Amlodipine 4 mg/5 mg tablets
Perindopril/Amlodipine 4 mg/10 mg tablets
Perindopril/Amlodipine 8 mg/5 mg tablets
Perindopril/Amlodipine 8 mg/10 mg tablets
Perindopril tert-butylamine/Amlodipine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Perindopril/Amlodipine is and what it is used for
2. Before you take Perindopril/Amlodipine
3. How to take Perindopril/Amlodipine
4. Possible side effects
5. How to store Perindopril/Amlodipine
6. Further information

1. WHAT PERINDOPRIL/AMLODIPINE IS AND WHAT IT IS USED FOR

Perindopril/Amlodipine is prescribed for treatment of high blood pressure (hypertension) and/or treatment of stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked).
Patients already taking perindopril and amlodipine from separate tablets may instead receive one tablet of Perindopril/Amlodipine which contains both ingredients.

Perindopril/Amlodipine is a combination of two active ingredients, perindopril and amlodipine. Perindopril is an ACE (angiotensin converting enzyme) inhibitor. Amlodipine is a calcium antagonist (which belongs to a class of medicines called dihydropyridines). Together they work to widen and relax the blood vessels, which results in a reduction of blood pressure. Blood can flow through the body more easily and the heart does not need to work so hard.

2. BEFORE YOU TAKE PERINDOPRIL/AMLODIPINE

Do not take Perindopril/Amlodipine
- if you are allergic (hypersensitive) to perindopril tert-butylamine or any other ACE inhibitor, amlodipine besylate or any other dihydropyridines, or any of the other ingredients of Perindopril/Amlodipine (see section 6 for list of ingredients).
- if you are more than 3 months pregnant. (It is also better to avoid Perindopril/Amlodipine in early pregnancy – see pregnancy section.).
- if you have experienced symptoms such as wheezing, swelling of the face or tongue, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema).
- if you have cardiogenic shock (when the heart is unable to supply sufficient blood to the body), aortic stenosis (narrowing of the main blood vessels leading from the heart) or unstable angina (chest pain that may occur when resting).
- if you have severe low blood pressure (severe hypotension),
- if you suffer from heart failure (the heart fails to pump blood adequately resulting in the shortness of breath or peripheral swellings such as swelling of the legs, ankles or feet) after an acute heart attack.

**Take special care with Perindopril/Amlodipine**
- if you have hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery which supplies the kidney with blood),
- if you have any other heart problems,
- if you have impaired liver function,
- if you have kidney problems or if you are receiving dialysis,
- if you have collagen vascular disease (disease of the connective tissue) such as systemic lupus erythematosus or scleroderma,
- if you have diabetes,
- if you are on a salt restricted diet or use salt substitutes which contain potassium (a well balanced potassium blood level is essential).

You must tell your doctor if you think you are (or might become) pregnant. Perindopril/Amlodipine is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

When you are taking Perindopril/Amlodipine, you should also inform your doctor or the medical staff if you:
- are going to have a general anaesthetic and/or major surgery,
- have recently suffered from diarrhoea or vomiting (being sick),
- are to undergo LDL apheresis (the removal of cholesterol from your blood by a machine),
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings.

Perindopril/Amlodipine is not recommended for use in children and adolescents.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should avoid Perindopril/Amlodipine with:
- lithium (used to treat mania or depression),
- estramustine (used in cancer therapy),
- potassium-sparing diuretics (spironolactone, triamterene), potassium supplements or salt substitutes containing potassium.

Treatment with Perindopril/Amlodipine can be affected by other medicines. Make sure to tell your doctor if you are taking any of the following medicines as special care may be required:
- other medicines for high blood pressure, including diuretics (medicines which increase the amount of urine produced by the kidneys),
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for pain relief or high dose acetylsalicylic acid,
- medicines to treat diabetes (such as insulin),
- medicines to treat mental disorders such as depression, anxiety, schizophrenia etc (e.g. tricyclic antidepressants, antipsychotics, imipramine-like antidepressants, neuroleptics),
- immunosuppressants (medicines which reduce the defence mechanism of the body) used for the treatment of auto-immune disorders or following transplant surgery (e.g. ciclosporin),
- allopurinol (for the treatment of gout),
- proclainamide (for the treatment of an irregular heart beat),
- vasodilators including nitrates (products that widen the blood vessels),
- heparin (medicines used to thin blood),
- ephedrine, noradrenaline or adrenaline (medicines used to treat low blood pressure, shock or
asthma),
- baclofen used to treat muscle stiffness in diseases such as multiple sclerosis,
- some antibiotics such as rifampicin,
- antiepileptic agents such as carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone,
- itraconazole, ketoconazole (medicines used for treatment of fungal infections).
- alpha-blockers used for the treatment of enlarged prostate such as prazosin, alfuzosin, doxazosin, tamsulosin, terazosin,
- amifostine (used to prevent or reduce side effects caused by other medicines or radiation therapy that are used to treat cancer),
- corticosteroids (used to treat various conditions including severe asthma and rheumatoid arthritis),
- gold salts, especially with intravenous administration (used to treat symptoms of rheumatoid arthritis).

**Taking Perindopril/Amlodipine with food and drink**

Perindopril/Amlodipine should be taken before a meal.

**Pregnancy and breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine.

**Pregnancy**

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Perindopril/Amlodipine before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril/Amlodipine. Perindopril/Amlodipine is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

**Breastfeeding**

Tell your doctor if you are breast-feeding or about to start breast-feeding. Perindopril/Amlodipine is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

**Driving and using machines**

Perindopril/Amlodipine does not affect alertness but you might experience dizziness or weakness due to low blood pressure which could affect your ability to drive or operate machinery. You are advised not to drive a car or operate machinery until you know how Perindopril/Amlodipine affects you.

3. **HOW TO TAKE PERINDOPRIL/AMLODIPINE**

Always take Perindopril/Amlodipine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Swallow your tablet with a glass of water, preferably at the same time each day, in the morning, before a meal. Your doctor will decide on the correct dose for you. This will normally be one tablet per day. Perindopril/Amlodipine will usually be prescribed for patients already taking perindopril and amlodipine from separate tablets.

**If you take more Perindopril/Amlodipine than you should**

If you take too many tablets, contact your nearest accident and emergency department or tell your doctor immediately. The most likely symptoms of overdose are low blood pressure which can make you feel dizzy or faint. If this happens, lying down with your legs raised can help.

**If you forget to take Perindopril/Amlodipine**

It is important to take your medicine every day as regular treatment works better. However, if you
forget to take a dose of Perindopril/Amlodipine, take the next dose at the usual time.
Do not take a double dose to make up for a forgotten tablet.

If you stop taking Perindopril/Amlodipine
As the treatment with Perindopril/Amlodipine is usually life-long, you should discuss with your doctor before you stop taking your tablets.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Perindopril/Amlodipine can cause side effects, although not everybody gets them.

Side effects are classified into the following groups in order of frequency:

<table>
<thead>
<tr>
<th>Very common:</th>
<th>Affects more than 1 user in 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>Rare:</td>
<td>Affects 1 to 10 users in 10,000</td>
</tr>
<tr>
<td>Very rare:</td>
<td>Affects less than 1 ser in 10,000</td>
</tr>
<tr>
<td>Not known:</td>
<td>Frequency cannot be estimated from available data</td>
</tr>
</tbody>
</table>

If you experience any of the following, stop taking the medicinal product at once and tell your doctor immediately:
- symptoms of allergic reaction such as swelling of the face, lips, mouth, tongue or throat, difficulty in breathing,
- severe dizziness or fainting,
- unusual fast or irregular heart beat.

Other side effects include:
- Common side effects (occur in less than 1 in 10 users but in more than 1 in 100 users):
  - headache, dizziness, vertigo, pins and needles, somnolence (sleepiness), vision disturbances, tinnitus (sensation of noises in the ears), palpitations (very fast heartbeat), flushing (hot or warm feeling in your face), light-headedness due to low blood pressure, cough, shortness of breath, nausea (feeling sick), vomiting (being sick), abdominal pain, taste disturbances, dyspepsia or difficulty of digestion, diarrhoea, constipation, allergic reactions (such as skin rashes, itching), muscle cramps, feeling of tiredness, oedema (swelling of your legs or ankles),

- Uncommon side effects (occur in less than 1 in 100 users but in more than 1 in 1000 users):
  - mood swings, sleep disturbances, trembling, syncope (temporary loss of consciousness), loss of pain sensation, rhinitis (blocked up or runny nose), changed bowel habits, hair loss, red or discoloured patches on skin, back, muscle or joint pain, chest pain, increased need to urinate especially during the night, malaise (general feeling of being unwell), bronchospasm (tightening of the chest, wheezing and shortness of breath), dry mouth, angioedema (symptoms such as wheezing, swelling of the face or tongue), kidney problems, impotence, increased sweating, breast enlargement in men, weight increase or decrease,

- Very rare side effects (occur in less than 1 in 10,000 users):
  - confusion, cardiovascular disorders (irregular heart beat, angina, heart attack and stroke), eosinophilic pneumonia (a rare type of pneumonia), erythema multiforme (a skin rash which often starts with red itchy patches on your face, arms or legs), disorders of the blood, pancreas, stomach or liver, peripheral neuropathy (disease that produces loss of sensations, pain, inability to control muscles), hypertonia (abnormal increase in muscle tension), vasculitis (inflammation of blood vessels of the skin), swelling of the gums, high blood sugar.

The following side effects have also been reported by patients taking Perindopril/Amlodipine:
hypoglycaemia (very low blood sugar level), vasculitis (inflammation of blood vessels).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PERINDOPRIL/AMLODIPINE

Keep out of the reach and sight of children.

Do not use Perindopril/Amlodipine after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Perindopril/Amlodipine contains
- The active substances are perindopril tert-butylamine and amlodipine.
  Perindopril/Amlodipine 4 mg/5 mg tablets
  Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 mg perindopril) and 5 mg amlodipine (as besilate).
  Perindopril/Amlodipine 4 mg/10 mg tablets
  Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 g perindopril) and 10 mg amlodipine (as besilate).
  Perindopril/Amlodipine 8 mg/5 mg tablets
  Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 5 mg amlodipine (as besilate).
  Perindopril/Amlodipine 8 mg/10 mg tablets
  Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 10 mg amlodipine (as besilate).
- The other ingredients are sodium hydrogen carbonate, microcrystalline cellulose (E460), pregelatinised maize starch, sodium starch glycolate (type A), colloidal anhydrous silica and magnesium stearate (E572).

What Perindopril/Amlodipine looks like and contents of the pack
Perindopril/Amlodipine 4 mg/5 mg tablets: this medicinal product is presented as white to almost white, round, slightly biconvex tablets with bevelled edges.
Perindopril/Amlodipine 4 mg/10 mg tablets: this medicinal product is presented as white to almost white, capsule shaped, biconvex tablets scored on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
Perindopril/Amlodipine 8 mg/5 mg tablets: this medicinal product is presented as white to almost white, round, biconvex tablets with bevelled edges.
Perindopril/Amlodipine 8 mg/10 mg tablets: this medicinal product is presented as white to almost white, round, biconvex tablets with bevelled edges and a score line on one side. The tablet can be divided into equal halves.

The tablets are available in carton boxes of 5, 7, 10, 14, 20, 28, 30, 50, 60, 90 and 100 tablets in blisters.
Not all pack sizes may be marketed.
Marketing Authorisation Holder
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8000 Novo mesto, Slovenia

Manufacturers
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
TAD Pharma GmbH, Heinz-Lohmann-Str.5, 27472 Cuxhaven, Germany

This leaflet was last approved in
06/2011
Module 4
Labelling

The following text is the approved label text. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX/for blisters

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Amlodipine 4 mg/5 mg tablets
Perindopril/Amlodipine 4 mg/10 mg tablets
Perindopril/Amlodipine 8 mg/5 mg tablets
Perindopril/Amlodipine 8 mg/10 mg tablets

Perindopril tert-butylamine/Amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 mg perindopril) and 5 mg amlodipine (as besilate).
Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 mg perindopril) and 10 mg amlodipine (as besilate).
Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 5 mg amlodipine (as besilate).
Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 10 mg amlodipine (as besilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5 tablets
7 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

4 mg/5 mg tablets: PL01656/0114
4 mg/10 mg tablets: PL01656/0115
8 mg/5 mg tablets: PL01656/0116
8 mg/10 mg tablets: PL01656/0117

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Perindopril/Amlodipine 4 mg/5 mg tablets
PAR Perindopril/Amlodipine 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets
UN/H/4348 & 4620-1/001-4/DC

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER/ OPA/Al/PVC//Al foil

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Amlodipine 4 mg/5 mg tablets
Perindopril/Amlodipine 4 mg/10 mg tablets
Perindopril/Amlodipine 8 mg/5 mg tablets
Perindopril/Amlodipine 8 mg/10 mg tablets
Perindopril tert-butylamine/Amlodipine

2. NAME OF THE MARKETING AUTHORITY/HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX/for blisters

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Amlodipine 4 mg/5 mg tablets
Perindopril/Amlodipine 4 mg/10 mg tablets
Perindopril/Amlodipine 8 mg/5 mg tablets
Perindopril/Amlodipine 8 mg/10 mg tablets
Perindopril tert-butylamine/Amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 mg perindopril) and 5 mg amlodipine (as besilate).
Each tablet contains 4 mg perindopril tert-butylamine (equivalent to 3.34 mg perindopril) and 10 mg amlodipine (as besilate).
Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 5 mg amlodipine (as besilate).
Each tablet contains 8 mg perindopril tert-butylamine (equivalent to 6.68 mg perindopril) and 10 mg amlodipine (as besilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5 tablets
7 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

4 mg/5 mg tablets: PL01656/0133
4 mg/10 mg tablets: PL01656/0134
8 mg/5 mg tablets: PL01656/0135
8 mg/10 mg tablets: PL01656/0136

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRaille

Perindopril/Amlodipine 4 mg/5 mg tablets
Perindopril/Amlodipine 4 mg/10 mg tablets
Perindopril/Amlodipine 8 mg/5 mg tablets
Perindopril/Amlodipine 8 mg/10 mg tablets
## MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**BLISTER/ OPA/Al/PVC//Al foil**

### 1. NAME OF THE MEDICINAL PRODUCT

- Perindopril/Amlodipine 4 mg/5 mg tablets
- Perindopril/Amlodipine 4 mg/10 mg tablets
- Perindopril/Amlodipine 8 mg/5 mg tablets
- Perindopril/Amlodipine 8 mg/10 mg tablets
- Perindopril tert-butylamine/Amlodipine

### 2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

### 3. EXPIRY DATE

EXP

### 4. BATCH NUMBER

Batch

### 5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX/for blisters

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Amlodipine 4 mg/5 mg tablets
Perindopril/Amlodipine 4 mg/10 mg tablets
Perindopril/Amlodipine 8 mg/5 mg tablets
Perindopril/Amlodipine 8 mg/10 mg tablets
Perindopril tert-butyamine/Amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4 mg perindopril tert-butyamine (equivalent to 3.34 mg perindopril) and 5 mg amlodipine (as besilate).
Each tablet contains 4 mg perindopril tert-butyamine (equivalent to 3.34 mg perindopril) and 10 mg amlodipine (as besilate).
Each tablet contains 8 mg perindopril tert-butyamine (equivalent to 6.68 mg perindopril) and 5 mg amlodipine (as besilate).
Each tablet contains 8 mg perindopril tert-butyamine (equivalent to 6.68 mg perindopril) and 10 mg amlodipine (as besilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5 tablets
7 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORIZATION NUMBER(S)

4 mg/5 mg tablets: PL01656/0137
4 mg/10 mg tablets: PL01656/0138
8 mg/5 mg tablets: PL01656/0139
8 mg/10 mg tablets: PL01656/0140

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
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<tbody>
<tr>
<td>BLISTER/ OPA/Al/PVC/Al foil</td>
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<table>
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<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<td>Perindopril tert-butylamine/Amlodipine</td>
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<table>
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<th>5. OTHER</th>
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Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Perindopril/Amlodipine 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets (PL 01656/0114-7 & 0133-40; UK/H/4348 & 4620-1/001-4/DC) could be approved. These applications were submitted by the Decentralised Procedure, with the UK as Reference Member State (RMS), and Czech Republic, Spain, France, Hungary, Italy, Lithuania, Latvia, the Netherlands, Poland, Portugal, Romania, Slovenia and Slovakia as Concerned Member States (CMS).

Perindopril/Amlodipine 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets are prescription-only medicines (POM) 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.

These are applications made according to Article 10(b) of Directive 2001/83/EC, as amended, applicable for a fixed combination product of known active substances. Under Article 7 of the Paediatric Regulation, the following waivers apply to these applications and copies of these waivers have been supplied:

- A class-specific waiver for the proposed indication of coronary artery disease is covered by EMEA class waiver decision P/63/2010 for products indicated for coronary atherosclerosis.
- A product-specific waiver for the proposed indication of hypertension is covered by EMEA-000983-PIP01-10.

Perindopril/Amlodipine tablets contain the active ingredients perindopril tert-butylamine and amlodipine besilate.

Perindopril is an inhibitor of Angiotensin Converting Enzyme (ACE), the enzyme that converts angiotensin I into angiotensin II. 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.

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully understood, but is determined by the following two actions:
1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilatation increases the supply in oxygen to myocardium in patients with Prinzmetal’s angina attack.
No new non-clinical studies were conducted, which is acceptable given that the applications were for fixed combination products containing well-known active substances.

One single-dose, bioequivalence study was submitted to support these applications, comparing the test product Perindopril/Amlodipine 8 mg/10 mg tablets with the reference products Prexanil 8 mg (Les Laboratoires Servier Industrie, France) and Istin 10 mg tablets (Heinrich Mack Nachf. GmbH & Co. KG, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The Marketing Authorisation Holder has presented scientific arguments to demonstrate that there is no relevant pharmacokinetic interaction between the two components, based on published data including the lack of mention of interaction in the respective SmPCs and based on the bioequivalence study submitted. In addition, the Marketing Authorisation Holder has submitted an interaction study (FK interaction study - ClinOth000726) to support these applications.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved, with the end of procedure (Day 210) on 22 June 2011.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Perindopril/Amlodipine 4 mg/5 mg tablets  
Perindopril/Amlodipine 4 mg/10 mg tablets  
Perindopril/Amlodipine 8 mg/5 mg tablets  
Perindopril/Amlodipine 8 mg/10 mg tablets |
<table>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Perindopril tert-butylamine and amlodipine besilate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Agents acting on the renin-angiotensin system, ACE inhibitors and calcium channel blockers (ATC code: C09 BB04.)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/4348 &amp; 4620-1/001-4/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
| Member States concerned                     | UK/H/4348/001-4/DC: Czech Republic, Spain, Hungary, Italy, Lithuania, Latvia, the Netherlands, Poland, Portugal, Romania, Slovenia and Slovakia.  
UK/H/4621/001-4/DC: Czech Republic, Hungary, Lithuania, Poland, Slovenia and Slovakia. |
| Marketing Authorisation Number(s)            | PL 01656/0114-7 & 0133-40                                                            |
| Name and address of the authorisation holder | KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8000 Novo mesto, Slovenia                |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substances

The product contains two active substances, perindopril tert-butylamine and amlodipine besilate.

(1) Perindopril tert-butylamine

INN: Perindopril erbumine
Synonyms: Perindopril tert-butylamine
Chemical name: 2-Methylpropan-2-amine (2S,3aS,7aS)-1-((S)-2-((S)-1-ethoxy-1-oxopentan-2-ylamino)propanoyl)octahydro-1H-indole-2-carboxylate

Structure:

Molecular formula: C_{23}H_{43}N_{3}O_{5}
Molecular weight: 441.6
Appearance: Preindopril erbumine is a white or almost-white crystalline powder.

(2) Amlodipine besilate

INN: Amlodipine besilate
Chemical name: 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate

Structure:

Molecular formula: C_{20}H_{25}ClN_{2}O_{5}.C_{6}H_{6}O_{3}S
Molecular weight: 567.06
Appearance: Amlodipine besilate is a white or almost-white powder. Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol and slightly soluble in 2-propanol.

Both active substances are the subject of European Pharmacopoeia monographs.

All aspects of the manufacture and control of amlodipine besilate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Synthesis of the active substance perindopril tert-butylamine from the designated starting materials has been adequately described, and appropriate in-process controls and
intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate specifications are provided for the active substance perindopril tert-butylamine. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance perindopril tert-butylamine. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specifications.

Suitable specifications have been provided for all packaging used for the active substance perindopril tert-butylamine. The primary packaging has been shown to comply with current guidelines concerning contact with food. For this active substance, appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium hydrogen carbonate, microcrystalline cellulose (E460), pregelatinised maize starch, sodium starch glycolate (type A), colloidal anhydrous silica and magnesium stearate (E572).

Appropriate justifications for the inclusion of each excipient have been provided.

All excipients used comply with their respective European Pharmacopoeia monograph Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

Pharmaceutical Development

The objective of the development programme was to combine the currently approved doses of the active substances perindopril tert-butylamine and amlodipine besilate into a robust, stable, single tablet intended to support patient adherence to treatment. A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and reference products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated on production-scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and these comply with the release specifications. Certificates of analysis have been provided for all working standards used.
Container-Closure System
All strengths of the finished product are packaged in olefin polyamide/aluminium/polyvinylchloride blister strips and are available in pack sizes of 5, 7, 10, 14, 20, 28, 30, 50, 60, 90 and 100 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the Product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions ‘Store in the original package in order to protect from light and moisture.’

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

MAA Forms
The MAA forms are satisfactory.

Expert Report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of amlodipine and perindopril are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.
A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.

**III.3 CLINICAL ASPECTS**

**Pharmacokinetics**

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, single dose, two period, two-sequence, two-way crossover, study to compare the pharmacokinetics of the test product Perindopril/Amlodipine 8 mg/10 mg tablets versus co-administration of the reference products Prexanil 8 mg (Les Laboratoires Servier Industrie, France) and Istin 10 mg tablets (Heinrich Mack Nachf. GmbH & Co. KG, Germany) in healthy adult male volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or the co-administered mono component reference products with 240 ml of water under fasting conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period between treatment periods was at least 35 days.

The pharmacokinetic results for perinopril are presented below (non-transformed values; arithmetic mean ± SD, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-t}$ ng/ml/h</th>
<th>$AUC_{0-\infty}$ ng/ml/h</th>
<th>$C_{max}$ ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test ± Standard Deviation (SD)</td>
<td>84.82± 19.77</td>
<td>85.76 ±19.85</td>
<td>73.19 ± 19.57</td>
</tr>
<tr>
<td>Reference ± Standard Deviation (SD)</td>
<td>82.48± 19.71</td>
<td>83.32± 19.74</td>
<td>71.52 ± 18.63</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-t}$ ng/ml/h</th>
<th>$AUC_{0-72}$ ng/ml/h</th>
<th>$C_{max}$ ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test ± Standard Deviation (SD)</td>
<td>159.72±45.94</td>
<td>161.81±47.68</td>
<td>11.30±5.53</td>
</tr>
<tr>
<td>Reference ± Standard Deviation (SD)</td>
<td>153.46±40.25</td>
<td>155.07±40.99</td>
<td>11.23±5.18</td>
</tr>
</tbody>
</table>

*ln-transformed values

The pharmacokinetic results for perinoprilat are presented below (non-transformed values; arithmetic mean ± SD, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-72}$ ng/ml/h</th>
<th>$AUC_{0-\infty}$ ng/ml/h</th>
<th>$C_{max}$ ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test ± Standard Deviation (SD)</td>
<td>102.45 (98.23-106.86%)</td>
<td>103.80 (99.82-107.93%)</td>
<td>99.12 (98.23-106.86%)</td>
</tr>
<tr>
<td>Reference ± Standard Deviation (SD)</td>
<td>102.45 (98.23-106.86%)</td>
<td>103.80 (99.82-107.93%)</td>
<td>99.12 (98.23-106.86%)</td>
</tr>
</tbody>
</table>

*ln-transformed values
The pharmacokinetic results for amlodipine are presented below (non-transformed values; arithmetic mean ± SD, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(\text{AUC}_{0-72}) ng/ml/h</th>
<th>(\text{C}_{\text{max}}) ng/ml</th>
<th>(\text{T}_{\text{max}}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test ± Standard Deviation (SD)</td>
<td>231735.8 ± 66538.1</td>
<td>5884.74 ± 1400.19</td>
<td>7.11 ± 2.59</td>
</tr>
<tr>
<td>Reference ± Standard Deviation (SD)</td>
<td>221839.1 ± 59113.9</td>
<td>5760.79 ± 1284.84</td>
<td>7.26 ± 2.53</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>104.07 (101.07-107.17%)</td>
<td>101.76 (98.87-104.73%)</td>
<td>-</td>
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</tbody>
</table>

AUC\(_{0-72}\) area under the plasma concentration-time curve from time zero to 72 hours

\(\text{C}_{\text{max}}\) maximum plasma concentration

\(\text{T}_{\text{max}}\) time to maximum concentration of drug in serum

*ln-transformed values

The 90% confidence intervals for AUC and \(\text{C}_{\text{max}}\) for test versus reference products for perindopril, perindoprilat and amlodipine are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product is bioequivalent to the reference products.

As the 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions of the bioequivalence study on the 8 mg/10 mg strength can be extrapolated to the other strengths.

The Marketing Authorisation Holder has also submitted the following interaction study (FK interaction study- ClinOth000726) to support these applications:

An open-label, randomised, two-way crossover, two-sequence study in parallel cohorts to assess the single-dose pharmacokinetics of Amlodipine Besylate 10 mg Tablets and Perindopril Erbumine 8 mg Tablets when administered together or alone, in healthy adult male volunteers under fasted conditions.

All volunteers received a single oral dose of the one 8 mg Perindopril Erbumine Tablet (Prexanil®), one 10 mg Amlodipine Tablet (Norvasc®) or a single oral dose of the one 8 mg Perindopril Erbumine Tablet (Prexanil®) and a single oral dose of one 10 mg Amlodipine Tablet (Norvasc®) with 240 ml of water. The washout period between treatment periods was at least 35 days.

The 90% confidence intervals (CI) of the ratios of least-squares means (LSM) for amlodipine in plasma derived from the analyses of the ln-transformed pharmacokinetics parameters AUC\(_{0-t}\) and \(\text{C}_{\text{max}}\) of amlodipine and perindopril administered together compared to amlodipine administered alone, were within the 80.00 – 125.00% no interaction range. Based on these results, perindopril erbumine does not affect the pharmacokinetics of amlodipine.

The 90% CIs of the ratios of LSM for perindopril and perindoprilat in plasma derived from the analyses of the ln-transformed pharmacokinetics parameters AUC\(_{0-t}\) and \(\text{C}_{\text{max}}\) of amlodipine and perindopril administered together compared to perindopril administered alone, were within the 80.00 – 125.00% no interaction range. Based on these results, amlodipine besylate does not affect the PK of perindopril and perindoprilat.
Based on the evaluation, no interaction was noted between amlodipine and perindopril using the specified design (FDC vs amlodipine and FDC vs perindopril). The 90% CI from both comparisons were within the 80-125% acceptance criteria used for bioequivalence.

**Pharmacodynamics**

No new pharmacodynamic data were submitted and none were required for these applications. This is in agreement with the requirements stated in the document CHMP/EWP/191583/2005 entitled “Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention”.

**Efficacy**

No new efficacy data were submitted and none were required for these applications. However, the Marketing Authorisation Holder has discussed data on the efficacy of perindopril and amlodipine combination through the results of the following clinical studies in addition to the trials of the individual agents:

- the ASCOT BPLA (The Anglo Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm) study
- the CAFE (the Conduit Artery Function Evaluation) study a sub study of ASCOT
- and a third open label study in 500 asian Indians.

The main considerations are therefore evidence of well established use of the free combination. The applicant has persuasively argued this is the case and provided supporting evidence from IMS MIDAS (Intercontinental Marketing Services) database from 5 European Union markets.

**Safety**

With the exception of the data generated during the bioequivalence study and the interaction study no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data or the interaction study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**

The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

**Clinical Expert Report**

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.
Conclusion
There are no objections to the approval of these applications from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Perindopril/Amlodipine 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of perindopril and amlodipine are well-known.

Considering the extensive knowledge on the non-clinical data for perindopril and amlodipine, and given human experience of their individual and combined use, it can be stated that the new fixed combinations perindopril tert-butylamine/amloptine do not raise any new non-clinical concerns.

EFFICACY AND SAFETY
With the exception of the bioequivalence study and the interaction study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Perindopril/Amlodipine 8 mg/10 mg tablets and the mono component reference products administered separately (Prexanil 8 mg and Istin 10 mg tablets). As the 4 mg/5 mg, 4 mg/10 mg, 8 mg/5 mg and 8 mg/10 mg strengths of the product meet the biowaiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions of the bioequivalence study on the 8 mg/10 mg strength can be extrapolated to the other strength tablets.

The clinical safety of the individual components, perindopril and amlodipine has been well established. Further evidence of safety is gleaned from the ASCOT trial. The IMS MIDAS dataset establishes increased use of the combination and absence of any safety related regulatory action.

No new or unexpected efficacy or safety concerns arose from the data submitted for the bioequivalence study or the interaction study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified.

The bioequivalence study supports the claim that the applicant’s fixed combination products are bioequivalent with the free mono components given separately at the same dose level and that there is no interaction between the two active substances. The Marketing Authorisation Holder has provided adequate justification for the combination product and the studies supporting these applications and these were acceptable.
Extensive clinical experience with perindopril and amlodipine in combination is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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