Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Perindopril Tosilate/Amlodipine Teva B.V. 5 mg/10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg perindopril tosilate equivalent to 3.408 mg perindopril converted *in situ* to perindopril sodium and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine.

Excipient with known effect
Each Perindopril Tosilate/Amlodipine Teva B.V. 5 mg/10 mg tablet contains 86.6 mg of isomalt:
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, round, biconvex tablet, debossed "5/10" on one side and plain on the other side.
Dimensions: Approx. 7 mm diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Perindopril Tosilate/Amlodipine Teva B.V. 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

Posology

One tablet per day as a single dose, preferably in the morning and before a meal.

The fixed dose combination is not suitable for initial therapy.
If a change of posology is required, the dose of the perindopril and amlodipine combination could be modified or individual titration with free combination may be considered.

Special populations

Patients with renal impairment and elderly (see sections 4.4 and 5.2)
Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the routine medical follow-up will include frequent monitoring of creatinine and potassium.

The combination of perindopril and amlodipine can be administered in patients with Clcr ≥ 60ml/min, but is not recommended in patients with a Clcr < 60ml/min. In these patients, an individual dose titration with the mono-components is recommended.

Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Amlodipine is not dialysable.

Concomitant use of perindopril with alikiren is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73m^2), see section "Contraindications".

Patients with hepatic impairment (see sections 4.4 and 5.2)

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

Paediatric population
The combination of perindopril and amlodipine should not be used in children and adolescents as the efficacy and tolerability of perindopril and amlodipine, or in combination, have not been established.

Method of administration:
For oral use.

4.3 Contraindications

Linked to perindopril:

- Hypersensitivity to the active substances or to any other ACE inhibitor
- History of angioedema associated with previous ACE inhibitor therapy (see section 4.4)
- Hereditary or idiopathic angioedema,
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Patients with diabetes mellitus or renal impairment (GFG <60 ml/min/1.73 m^2), the combination of perindopril and amlodipine should not be used in combination with products containing aliskiren (see sections 4.5 and 5.1)
- Concomitant use with sakubitril/valsartan (see sections 4.4 and 4.5)
- Extracorporeal treatment which causes blood to interact with negatively charged surfaces (see section 4.5)
- Significant renal artery stenosis or stenosis of a single functioning renal artery (see section 4.4)

Linked to amlodipine

- Hypersensitivity to amlodipine or to any other dihydropyridine derivatives
- Severe hypotension
- 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 Tosilate/Amlodipine Teva B.V.
All contraindications related to each mono-component, as listed above, should also apply to the fixed combination of perindopril and amlodipine.

- Hypersensitivity to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

All warnings related to each mono-component, as listed below, should apply also to the fixed combination of perindopril and amlodipine.

Linked to perindopril

Special warnings
Hypersensitivity/Angioedema:
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or the 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, the combination of perindopril and 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).

Concomitant use of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Treatment with sacubitril/valsartan must not be initiated until 36 hours after the last dose of perindopril. If treatment with sacubitril/valsartan is stopped, perindopril treatment must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5). Concomitant use of other NEP inhibitors (e.g racecadotril) with an ACE inhibitor may also increase the risk of angiodema (see section 4.5). Therefore, a careful assessment of the benefit to risk ratio is necessary before initiating a treatment with NEP inhibitors (e.g. racecadotril) in patients receiving perindopril.

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):
Patients receiving concomitant treatment with mTOR inhibitors (e.g.sirolimus, everolimus, temsirolimus) may be at increased risk of angioedema (swelling of the airways or tongue, with or without respiratory disturbance) (see section 4.5).

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 resumption of treatment.

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 risk factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Renovascular hypertension:
There is an increased risk of hypertension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors (see section 4.3). Treatment with diuretics can be a contributing factor. There may be loss of the renal function with only minor changes in serum creatinine, even in patients with unilateral renal artery stenosis.

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

Primary hyperaldosteronism
Patients with primary hyperaldosteronism do not generally respond to antihypertensive drugs which work by inhibiting the renin-angiotensin system. As a result, the use of this drug is not recommended in these patients.

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitors is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Precautions for use

Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients at high risk of symptomatic hypotension, blood pressure, renal function and serum potassium should be monitored closely during treatment with the combination of perindopril and 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 isotonic sodium chloride. Transient hypotension is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

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 mono-components is recommended (see section 4.2).
Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8).
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment.

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see section 4.8).

Race:
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.
As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough:

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

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, the combination of perindopril and 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.

Hyperkaliemia:
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, inter-current events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, cotrimoxazole also known as trimethoprim/sulfamethoxazole). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired real 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:

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

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

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

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

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

Linked to the combination of perindopril and amlodipine

All warnings related to each mono-component, as listed above, should apply also to the fixed combination of perindopril and amlodipine.

Precautions for use

Interactions
The concomitant use of the combination of perindopril and amlodipine with lithium, potassium-sparing diuretics or potassium supplements, or dantrolene is not recommended (see section 4.5).

Excipient(s):

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Isomalt
Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Linked to perindopril

Clinical trial data shows that, compared to a single agent acting on RAAS, double depression of the renin-angiotensin-aldosterone system (RAAS) with ACE combination of inhibitors, angiotension II receptor blockers, or aliskiren, associated with more common adverse events such as hypotension, hyperkalaemia and renal impairment (including acute renal failure) (see sections 4.3, 4.4 and 5.1).

Medicines that cause hyperkalaemia
Some medications or some classes of medications may increase hyperkalaemia risk, for example, aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor blockers, NSAIDs, heparins, immunosuppressant's (eg cyclosporine or tacrolimus), tripmethoprim and fixed dose combination with sulfamethoxazole (co-trimoxazole). The concomitant use of medicinal products increases the risk of hyperkalaemia.

Concomitant use contraindicated (see section 4.3):

Aliskiren:
In patients with diabetes or renal impairment, the risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Extracorporeal circulation treatment
Extracorporeal treatment that causes blood to interact with negatively charged surfaces, for example, using high-permeability membranes during dialysis or haemofiltration (e.g. polyacrylonitrile membranes) or low density lipoprotein apheresis with dextran sulfate may increase the risk of severe anaphylactoid reactions (see section 4.3). If such treatment is needed, it is necessary to use a different type of dialysis membrane or prescribe another class of antihypertensive drug.

Sacubitril/Valsartan
Perindopril should not be administered concomitantly with sacubitril / valsartan due to the ACE it may increase the risk of angioedema. Sacubitril/valsartan should not be initiated until 36 hours after the last dose of perindopril. Perindopril treatment is contraindicated within 36 hours of the last dose of sacubitil/valsartan (see sections 4.3 and 4.4).

Concomitant use not recommended:

Aliskiren
In patients not suffering from diabetes or renal impairment, the risk of hyperkalaemia, worsening of renal function, cardiovascular morbidity and mortality are increased.

Concomitant use with ACE inhibitors and angiotensin receptor blockers
It has been reported in literature that in patients with established atherosclerotic disease, heart failure or diabetes with end-organ damage, concomitant treatment with an ACE inhibitor and angiotensin receptor blocker has been associated with a higher frequency of hypotension, syncope, hyperkalaemia and worsening of renal function (including acute renal failure) compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g. by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of kidney function, potassium levels and blood pressure.

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

Cortimoxazole (trimethoprim/sulfamethaoxazole)
Patients receiving co-trimoxazole (trimethoprim / sulfamethoxazole) may be at risk of hyperkalaemia (see section 4.4).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
Hyperkalaemia (potentially life-threatening), particularly in a context of renal failure cumulative hyperkalaemic agents). The combination of perindopril with the medicines mentioned above is not recommended (see section 4.4). if concomitant use is indicated, however, these medicinal products should be used with caution and periodic monitoring of serum potassium should be performed. For the use of the spironolactone in heart failure, see below.

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

Concomitant use which requires special care:

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).

Non-potassium-sparing diuretics
The initiation of treatment with an ACE inhibitor may lead to an excessive reduction in patients taking diuretics, which lack fluid and or electrolytes in the body (blood pressure). The reductive risk of hypotensive effects is possible with discontinuation of diuretics, increased intake of fluids or salts before starting treatment with low, progressively increasing doses of perindopril.
In treatment of patients with arterial hypertension who have had previous diuretic therapy there may have been a reduction in the amount of electrolytes or fluids in the body, or the need to discontinue diuretics before starting ACE inhibitors (in which case potassium may be reintroduced later, non-adherent diuretics), or a low dose ACE inhibitor, possibly followed by a low dose with progressive increments.
In diuretic-treated patients with congestive heart failure, at the start of treatment, use a very low dose of an ACE inhibitor, possibly following a previous non-potassium related retention dose reduction of the diuretic.
In all cases, renal function should be monitored during the first few weeks of treatment with an ACE inhibitor creatinine concentrations.

Potassium sparing diuretics (eplerenone, spironolactone)
Eplerenone of spironolactone (12.5 mg to 50 mg doses) with low ACE inhibitors doses in patients with class II-IV heart failure (NYHA) and with an ejection fraction of less than 40% , previously treated with ACE inhibitors and loop diuretics, the risk of hyperkalaemia, which can be fatal, especially if the combination is not prescribed. Before initialling therapy with this combination, it is necessary to make sure that there is no hyperkalaemia and no kidney dysfunction. Initially (during the first month of treatment) careful monitoring of potassium and sodium is recommended to check creatinine blood levels once a week and then monthly measurements.

Racecadotril
ACE inhibitors (such as perindopril) are known to cause angioedema. This risk may be higher with racecadotril (a medicine used to stop diarrhea).

mTOR inhibitors (eg sirolimus, everolimus, temsirolimus)
Patients receiving concomitant treatment with mTOR inhibitors may be at increased risk of angioedema (see section 4.4).

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

hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Concomitant use to be taken into consideration:

Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin)
Patients at increased risk of angioedema due to decreased activity in the dipeptidyl peptidase IV (DPP-IV) caused by gliptins in patients co-treated with ACE inhibitors.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

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

Linked to amlodipine

Concomitant use not recommended:
Dantrolene (infusion)
In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Concomitant use which requires special care:
CYP3A4 inducers:
When co-administering known inducers of CYP3A4, the plasma concentration of amlodipine may vary.. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with potent CYP3A4 inducers (e.g. rifampicin, St. John's wort [hypericum perforatum]).

CYP3A4 inhibitors:
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Therefore clinical monitoring and dose adjustment may be required.

There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.

Concomitant use to be taken into consideration:

The hypotensive effects of amlodipine are additional to those of other drugs with antihypertensive properties.

Tacrolimus
There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, the administration of amlodipine to a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus if necessary.

mTOR (Mechanistic Target of Rapamycin) Inhibitors
Inhibitors of mTOR such as sirolimus, temsirolimus and everolimus are substrates are CYP3A. Since amlodipine is a weak inhibitor of CYP3A, it may increase exposure to mTOR inhibitors when used concomitantly.

Ciclosporin
No interaction studies were conducted with ciclosporin and amlodipine in health volunteers or other populations, with the exception of patients who have had kidney transplant patients, with varying increase in the minimum concentration of ciclosporin (from 0% to 40% in average). The rate of ciclosporin should be monitored in subjects who have had a renal transplant and receiving amlodipine and a reduction in the dose of ciclosporin should be considered if needed.

Simvastatin
Co-administration of repeated doses of 10 mg amlodipine with 80 mg simvastatin results in a 77% increase in simvastatin exposure with simvastatin alone. The daily dose of simvastatin should be limited to 20 mg in patients treated with amlodipine.

Other combinations:
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in hypotensive effects.

Linked to the combination of perindopril and amlodipine

Concomitant use which requires special care:
Baclofen
Increased antihypertensive effect. If necessary, monitor the blood pressure and adjust the dosage of the antihypertensive.

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 nitroglycerin 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, the combination of perindopril and amlodipine is not recommended during the first trimester of pregnancy. The combination of perindopril and amlodipine is contraindicated during the second and third trimesters of pregnancy.
The combination of perindopril and amlodipine is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue the combination of perindopril and amlodipine taking account the importance of this therapy for the mother.

Pregnancy:

Linked to perindopril

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

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

Linked to amlodipine

The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses (see section 5.3).Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding:

Linked to perindopril

Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Linked to amlodipine

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility:

Linked to perindopril

There is no effect on the reproductive function or fertility.

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

4.7 Effects on ability to drive and use machines

No studies on the effects of the combination of perindopril and amlodipine on the ability to drive and use machines have been performed.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients treated with amlodipine experience dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

a) Summary of safety profile
The most common side effects reported with perindopril and amlodipine use are: oedema, drowsiness, dizziness, headache (especially at the beginning of treatment), dysgeusia, paresthesia, visual defects (including diplopia), tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), dyspnoea, cough, abdominal pain, nausea, vomiting, dyspepsia, intestinal transit, diarrhoea, constipation, pruritis, rash, exanthema, swelling of the joint (swelling of the ankles), contractures muscle, fatigue and asthenia.

b) Tabulated list of adverse effects
The following undesirable effects have been observed in clinical trials and post-use marketing authorisation with perindopril or amlodipine given separately and ranked under the MedDRA classification by organ system and under the following frequency:

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

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	Perindopril
Infections and infestations	Rhinitis	Uncommon	Very rare
Blood and lymphatic System Disorders	Eosinophilia	-	Uncommon*
	Leukopenia/neutropenia (see section 4.4)	Very rare	Very rare
	Agranulocytosis or pancytopenia (see section 4.4)	-	Very rare
	Thrombocytopenia (see section 4.4)	Very rare	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)	-	Very rare
	Decrease in haemoglobin and haematocrit	-	Very rare
Immune System Disorders	Allergic reactions: Urticaria	Very rare	Uncommon
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	-	Rare
Metabolism and Nutrition Disorders	Hyperglycaemia	Very rare	-
	Hypoglycaemia (see sections 4.4 and 4.5)	-	Uncommon*
	Hyponatraemia	-	Uncommon*
	Hyperkalaemia, reversible on discontinuation (see section 4.4)	-	Uncommon*
Psychiatric disorders	Insomnia	Uncommon	-
	Mood changes (including anxiety)	Uncommon	Uncommon
	Depression	Uncommon	Uncommon
	Sleep disturbances-	-	Uncommon
Nervous System disorders	Drowsiness (especially at the beginning of the treatment)	Common	Uncommon*
	Dizziness (especially at the beginning of the treatment)	Common	Common
	Headache (especially at the beginning of the treatment)	Common	Common
	Dysgeusia	Uncommon	Common
	Tremor	Uncommon	-
	Hypoesthaesia Paresthaesia	Uncommon Uncommon	- Common
	Syncope	Uncommon	Uncommon*
	Hypertonia	Very rare	-
	Peripheral neuropathy	Very rare	-
	Extrapyramidal disorder	Not known	-
	Excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
	Confusion	Rare	Very rare
Eye Disorders	Visual disturbances	Common	Common
	Diplopia	-	Common
Ear and labyrinth disorders	Tinnitus	Uncommon	Common
	Vertigo	-	Common
	Fear of heights	-	Common
Cardiac Disorders	Palpitations	Common	Uncommon*
	Syncope	Uncommon	-
	Angina pain Angina pectoris (see section 4.4)	Rare -	- Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	Very rare	Very rare
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Uncommon	Very rare
	Tachycardia	-	Uncommon*
Vascular	Flushing	Common	Rare

Disorders	Hypotension (and effects related to hypotension)	Uncommon	Common
	Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
	Vasculitis	Very Rare	Uncommon*
	Raynaud's phenomenon	-	Not known
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Common	Common
	Cough	Uncommon	Common
	Bronchospasm	-	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastro-intestinal Disorders	Gingival hyperplasia	Very rare	-
	Abdominal pain, nausea	Common	Common
	Vomiting	Uncommon	Common
	Dyspepsia	Common	Common
	Altered bowel habits	Common	-
	Dry mouth	Uncommon	Uncommon
	Diarrhoea, constipation	Common	Common
	Pancreatitis	Very rare	Very rare
	Gastritis	Very rare	-
	Dysgeusia	-	Common
	Taste perversion	Uncommon	-
Hepato-biliary Disorders	Hepatitis, cholestatic jaundice Hepatitis either cytolytic or cholestatic (see section 4.4)	Very rare -	- Very rare
	Hepatic enzymes increased (mostly consistent with cholestasis)	Very rare	-
Skin and Subcutaneous Tissue Disorders	Quincke's oedema Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)	Very rare Very rare	- Uncommon
	Erythema multiform	Very rare	Very rare
	Alopecia	Uncommon	-
	Purpura	Uncommon	-
	Skin discoloration	Uncommon	Uncommon
	Increased sweating	Uncommon	Uncommon
	Itching	Uncommon	Common
	Hyperhidrosis	Uncommon	Uncommon
	Pruritus	Uncommon	Common
	Rash, exanthema	Uncommon	Common
	Urticaria	Uncommon	Uncommon
	Stevens-Johnson Syndrome	Very rare	-
	Toxic Epidermal Necrolysis	Not known	-
	Exfoliative dermatitis	Very rare	-
	Photosensitivity	Very rare	Uncommon*
	Psoriasis aggravation	-	Rare
	Pemphigoid	-	Uncommon*
Musculoskeletal And Connective Tissue Disorders	Ankle swelling	Common	-
	Arthralgia, myalgia	Uncommon	Uncommon*
	Muscle cramps	Common	Common
	Back pain	Uncommon	-
Renal and Urinary Disorders	Micturition disorder, nocturia, increased urinary frequency	Uncommon	-
	Renal impairment	-	Uncommon
	Anuria/Oliguria	-	Rare
	Acute renal failure	-	Rare
Reproductive System and Breast Disorders	Impotence	Uncommon	Uncommon
	Gynaecomastia	Uncommon	-
	Erectile dysfunction	Uncommon	Uncommon
General Disorders and Administration	Oedema	Very common	-

Site Condition	Peripheral oedema	-	Uncommon
	Fatigue	Common	-
	Chest pain	Uncommon	Uncommon *
	Asthenia		Common
	Pain	Uncommon	-
	Malaise	Uncommon	Uncommon*
	Pyrexia	-	Uncommon*
Investigations	Weight increase, weight decrease	Uncommon	-
	Serum bilirubin and liver enzymes elevation	-	Rare
	Increases in blood urea and serum creatinine (see section 4.4)	-	Uncommon*
	Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis)	Very rare	-
	Decreased haemoglobin and haematocrit decreased	-	Very rare
Injury, poisoning and procedural complications	Fall	-	Uncommon*

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

There is no information on overdosing with the combination of perindopril and amlodipine in humans.

For amlodipine, experience with intentional overdose in humans is limited.

Symptoms: available data suggest that a significant overdose could result in excessive peripheral vasodilation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

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

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

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

For perindopril, limited data are available for overdosage 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:

Mechanism of action

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

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

Pharmacodynamic effects

Hypertension:
Perindopril is active in all stages 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 humans, 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.

Data from clinical trials related to double blockade of the renin-angiotensin Aldosterone (RAAS)

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Amlodipine:

Mechanism of action

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Pharmacodynamic effects

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

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

Table 1. Incidence of significant clinical outcomes for CAMELOT					
Cardiovascular event rates, No. (%)				Amlodipine vs. placebo	
Outcomes	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value
Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	.002
Nonfatal MI					
Stroke or TIA	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37
Cardiovascular death	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15
Hospitalization for CHF	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27
Resuscitated cardiac arrest	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46
	0	4 (0.6)	1 (0.1)	NA	.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24

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

Use in patients with heart failure:
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.
A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.
In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Study on the preventive treatment of heart attack (ALLHAT):
A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.
A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke > 6 months prior to enrolment or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).
The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 (95% CI(0.90-1.07) p=0.65). Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs 7.7%, RR 1.38, (95% CI [1.25-1.52] p<0.001)). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy, RR 0.96 (95% CI [0.89-1.02] p=0.20).

Paediatric population (aged 6 years and older)
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg 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.

5.2 Pharmacokinetic properties

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

Perindopril:

Absorption

After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a pro-drug. 27 % of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields 5 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.

Distribution

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

Elimination

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

Special populations
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.

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

Amlodipine:

Absorption, distribution, plasma protein binding

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

Biotransformation/elimination

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

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

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

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 foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

No carcinogenicity has been observed in long term studies in rats and mice.

Amlodipine:

Reproductive 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.
Effect of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.
Carcinogenicity and mutagenicity
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.
Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Povidone K 30
Isomalt
Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

White opaque PP tablet container and white opaque PE stopper with desiccant insert equipped with a tamper-evident PE flow reducer.

Pack sizes of:
30 and multipacks containing 90 (3 packs of 30) tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/098/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th November 2021

10 DATE OF REVISION OF THE TEXT

August 2022