

Amopril 5mg/4mg Tablet
Amopril 5mg/8mg Tablet
Amopril 10mg/4mg Tablet
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Name of medicine

1. Amopril 5mg/4mg Tablet
2. Amopril 5mg/8mg Tablet
3. Amopril 10mg/4mg Tablet
4. Amopril 10mg/8mg Tablet

Each tablet contains

Active ingredient:

1. Amlopidine / Perindopril tert-butylamine, 5 mg / 4 mg, tablets
Each tablet contains 5 mg amlopidine equivalent to 6.94 mg amlopidine besilate and 4 mg perindopril tert-butylamine.
2. Amlopidine / Perindopril tert-butylamine, 5 mg / 8 mg, tablets
Each tablet contains 5 mg amlopidine equivalent to 6.94 mg amlopidine besilate and 8 mg perindopril tert-butylamine.
3. Amlopidine / Perindopril tert-butylamine, 10 mg / 4 mg, tablets
Each tablet contains 10 mg amlopidine equivalent to 13.87 mg amlopidine besilate and 4 mg perindopril tert-butylamine.
4. Amlopidine / Perindopril tert-butylamine, 10 mg / 8 mg, tablets
Each tablet contains 10 mg amlopidine equivalent to 13.87 mg amlopidine besilate and 8 mg perindopril tert-butylamine.

Excipients: Cellulose, Microcrystalline type 20XLM, Cellulose, Microcrystalline type 112, Sodium Starch Glycolate, type A, Silica, Colloidal Anhydrous, Magnesium Stearate

Product Description

1. Amlopidine / Perindopril tert-butylamine, 5 mg / 4 mg, tablets
White or almost white, round, biconvex uncoated tablets with a diameter 7 mm.
2. Amlopidine / Perindopril tert-butylamine, 5 mg / 8 mg, tablets
White or almost white, round, biconvex uncoated tablets, engraved “100” on one side and $\hat{S}$ ” on the other side, with a diameter 9 mm.
3. Amlopidine / Perindopril tert-butylamine, 10 mg / 4 mg, tablets
White or almost white, round, flat uncoated tablets, engraved “10” on one side, with a diameter 9 mm.
4. Amlopidine / Perindopril tert-butylamine, 10 mg / 8 mg, tablets
White or almost white, round, biconvex uncoated tablets, engraved “S” on one side, with a diameter 9.5 mm.

Indication

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

Recommended Dose

Posology

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

The fixed dose combination is not suitable for initial therapy.

If a change of posology is required, the dose of the Amopril could be modified or individual titration with free combination may be considered.

Special populations

Renal impairment and elderly

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

Amopril can be administered in patients with Clcr ≥ 60ml/min, and is not suitable for patients with Clcr < 60ml/min. In these patients, an individual dose titration with the monocomponents is recommended.

Amlopidine 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 amlopidine plasma concentrations are not correlated with degree of renal impairment. Amlopidine is not dialysable.

Concomitant use of perindopril with aliskiren is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m2)

Patients with hepatic impairment

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

Paediatric populations

Amopril should not be used in children and adolescents as the efficacy and tolerability of perindopril and amlopidine, in combination, have not been established in children and adolescents.

Route of Administration

Oral route.

Contraindication

Linked to perindopril:

- Hypersensitivity to the active substance or to any other ACE inhibitor
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy
- Concomitant use of Amopril with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²)
- Concomitant use with sacubitril/valsartan
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney
- Concomitant use with sacubitril/valsartan therapy. Perindopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan

Linked to amlopidine:

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

Linked to Combination of Perindopril and Amlopidine

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

- Hypersensitivity to any of the excipients

Warning and Precautions

INCREASED RISK OF BIRTH DEFECTS, FETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY.

Linked to perindopril

Special warnings:

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril. This may occur at any time during therapy. In such cases, the combination of perindopril and amlopidine 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.

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

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Sacubitril/ valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/ valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Concomitant use of other NEP inhibitors (e.g. perindopril) and ACE inhibitors may also increase the risk of angioedema. Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. rasecadotril) in patients on perindopril

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactoid reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Renovascular hypertension:

There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Primary aldosteronism:

Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

Pregnancy:

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

Precaution 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. 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 amlopidine.

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.

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 monocomponents is recommended.

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

Hepatic failure:

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

Race:

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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

Cough:

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

Surgery/Anaesthesia:

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

ACE inhibitors, including perindopril, can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Risk factors for the development of 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, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole), aldosterone antagonists or angiotensin-receptor blockers, the combination of potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, aldosterone antagonists or angiotensin-receptor blockers, 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 serum potassium and renal function should be monitored.

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.

Kidney transplantation:

There is no experience regarding the administration of perindopril in patients with a recent kidney transplantation.

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Linked to amlopidine:

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

Use in patients with cardiac failure:

Patients with heart failure should be treated with caution. Pulmonary oedema has been reported to be higher in patients with severe heart failure (NYHA class III and IV) treated with amlopidine. Calcium channel blockers, including amlopidine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with impaired hepatic function:

The half-life of amlopidine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlopidine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose.

Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Use in elderly patients:

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

Use in renal failure:

Amlopidine may be used in such patients at normal doses. Changes in amlopidine plasma concentrations are not correlated with degree of renal impairment. Amlopidine is not dialysable.

Linked to the combination of perindopril and amlopidine

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

Precautions for use

Excipients:

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

Interactions

The concomitant use of the combination of perindopril and amlopidine with lithium, potassium-sparing diuretics or potassium supplements, or dantrolene is not recommended.

Interaction with Other Medicaments

Linked to perindopril

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

Drugs inducing hyperkalaemia:

Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and fixed dose combination with sulfamethoxazole (Co-trimoxazole). The combination of these drugs increases the risk of hyperkalaemia.

Concomitant use contra-indicated:

Aliskiren:

In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Extracorporeal treatments:

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polycrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions. If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Sacubitril/valsartan:

The concomitant use of perindopril with sacubitril/valsartan is contra-indicated as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after taking the last dose of sacubitril/valsartan.

Concomitant use not recommended:

Aliskiren:

In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker:

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

Estramustine:

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

Co-trimoxazole (trimethoprim/sulfamethoxazole):

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia.

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

Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects).

The combination of perindopril with the above-mentioned drugs is not recommended. If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see below.

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. Care should also be taken when perindopril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/ sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of perindopril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Lithium:

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

Concomitant use which requires special care:

Antidiabetic agents (insulins, oral hypoglycaemic agents):

Concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

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:

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

In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE inhibitor must be initiated with a low dosage and progressively increased.

In diuretic-treated congestive heart failure, the ACE inhibitor should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE inhibitor therapy.

Potassium-sparing diuretics (eplerenone, spironolactone):

With eplerenone or spironolactone at doses between 12.5 mg to 50 mg by day and with low doses of ACE inhibitors: In the treatment of class II-IV heart failure (NYHA) with an ejection fraction <40%, and previously treated with ACE inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination. Before initiating the combination, check the absence of hyperkalaemia and renal impairment.

A close monitoring of the kalaemia and creatininemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Medicines increasing the risk of angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema. Concomitant use of ACE inhibitors with rasecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema.

Rasecadotril:

ACE inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with rasecadotril (a drug used against acute diarrhea).

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:

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.

Gliptines (linagliptine, saxagliptine, sitagliptine,

Fertility:

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

Effect on Ability to Drive and Use Machine

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 suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. Caution is recommended especially at the start of treatment.

Side Effects

Summary of safety profile

The most commonly reported adverse reactions with perindopril and amlodipine given separately are: oedema, somnolence, dizziness, headache (especially at the beginning of the treatment), dysgeusia, paraesthesia, visual impairment (including diplopia), tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), dyspnoea, cough, abdominal pain, nausea, vomiting, dyspepsia, change of bowel habit, diarrhoea, constipation, pruritus, rash, exanthema, joint swelling (ankle swelling), muscle spasms, fatigue, asthenia.

Tabulated list of adverse reactions:

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
Blood and lymphatic System Disorders	Leucopenia/neutropenia	Very rare	Very rare
	Agranulocytosis or pancytopenia	-	Very rare
	Thrombocytopenia	Very rare	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH	-	Very rare
	Decrease in haemoglobin and haematocrit	-	Very rare
	Eosinophilia	-	Uncommon
Immune System Disorders	Allergic reactions	Very rare	Uncommon
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)		Rare
Metabolism and Nutrition Disorders	Hyperglycaemia	Very rare	-
	Hypoglycaemia	-	Not known
	Hyperkalaemia, reversible on discontinuation	-	Uncommon
	Hyponatraemia	-	Uncommon
Psychiatric disorders	Insomnia	Uncommon	Uncommon
	Mood changes (including anxiety)	Uncommon	Uncommon
	Depression	Uncommon	-
	Sleep disturbances	-	Uncommon
	Confusion	Rare	Very rare
Nervous System disorders	Somnolence (especially at the beginning of the treatment)	Common	
	Dizziness (especially at the beginning of the treatment)	Common	Common
	Headache (especially at the beginning of the treatment)	Common	Common
	Dysgeusia	Uncommon	Common
	Tremor	Uncommon	-
	Hypoesthesia	Uncommon	-
	Paresthaesia	Uncommon	Common
	Syncope	Uncommon	Uncommon
	Confusional state	Rare	Very rare
	Hypertonia	Very rare	-
	Peripheral neuropathy	Very rare	-
	Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients	-	Very rare
	Vertigo	-	Common
	Extrapiramidal disorder	Not known	-
Eye Disorders	Visual disturbances (including diplopia)	Uncommon	Common
Ear and labyrinth disorders	Tinnitus	Uncommon	Common
	Vertigo	-	Common
Cardiac Disorders	Palpitation	Common	-
	Angina pectoris	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients	Very rare	Very rare
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Very rare	Very rare
Vascular Disorders	Flushing	Common	-
	Hypotension (and effects related to hypotension)	Uncommon	Common
	Stroke possibly secondary to excessive hypotension in high-risk patients	-	Very rare
	Vasculitis	Very rare	Not known
	Raynaud's phenomenon		Not known
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Uncommon	Common
	Rhinitis	Uncommon	Very rare
	Cough	Very rare	Common
	Bronchospasm	-	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastro-intestinal Disorders	Gingival hyperplasia	Very rare	-
	Abdominal pain, nausea	Common	Common
	Vomiting	Uncommon	Common
	Dyspepsia	Uncommon	Common
	Altered bowel habits	Uncommon	-
	Dry mouth	Uncommon	Uncommon
	Diarrhoea, constipation	Uncommon	Common
	Pancreatitis	Very rare	Very rare
	Gastritis	Very rare	-
Hepato-biliary Disorders	Hepatitis, jaundice	Very rare	-
	Hepatitis either cytolytic or cholestatic	-	Very rare
	Hepatic enzymes increased (mostly consistent with cholestasis)	Very rare	-
Skin and Subcutaneous Tissue Disorders	Quincke's oedema	Very rare	-
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx	Very rare	Uncommon
	Erythema multiforme	Very rare	Very rare
	Alopecia	Uncommon	-
	Purpura	Uncommon	-
	Skin discoloration	Uncommon	-
	Hyperhidrosis	Uncommon	Uncommon
	Pruritus	Uncommon	Common
	Rash, exanthema	Uncommon	Common
	Urticaria	Very rare	Uncommon
	Psoriasis aggravation	-	Rare
	Stevens-Johnson Syndrome	Very rare	-
	Exfoliative dermatitis	Very rare	-
	Photosensitivity	Very rare	-
	Pemphigoid	-	Uncommon
	Toxic Epidermal Necrolysis	Unknown	-
Musculoskeletal And Connective Tissue Disorders	Joint swelling (Ankle swelling)	Common	-
	Arthralgia, myalgia	Uncommon	-
	Muscle cramps/ muscle spasms	Uncommon	Common
	Back pain	Uncommon	-

Renal and Urinary Disorders	Micturition disorder, nocturia, increased urinary frequency, pollakiuria	Uncommon	-
	Renal impairment, renal failure	-	Uncommon
	Acute renal failure	-	Rare
	Anuria/Oliguria		Rare
Reproductive System and Breast Disorders	Impotence, erectile dysfunction	Uncommon	Uncommon
	Gynaecomastia	Uncommon	-
General Disorders and Administration Site Condition	Oedema	Common	-
	Oedema peripheral	-	Uncommon
	Fatigue	Common	-
	Chest pain	Uncommon	-
	Asthenia	Uncommon	Common
	Pain	Uncommon	-
	Malaise	Uncommon	-
	Pyrexia	-	Uncommon
Investigations	Weight increase, weight decrease	Uncommon	-
	Serum bilirubin and liver enzymes elevation	-	Rare
	Increases in blood urea and serum creatinine, hyperkalaemia	-	Not known
Injury, poisoning and procedural complication	Fall	-	Uncommon

Cases of SIADH have been reported with other ACE inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE inhibitor therapy including perindopril.

Additional information linked to amlodipine

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 the national reporting system.

Symptoms and Treatment of Overdose

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

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

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

Treatment: clinically significant hypotension due to amlodipine 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. The use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

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

Pharmacodynamics

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 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.

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:

From the available efficacy data on 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%. In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% was observed in the primary endpoint compared to placebo.

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.

Use in patients with heart failure:

Amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology in New York Heart Association (NYHA) Class II-IV heart failure patients

Amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure in patients with NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors

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.

Treatment to prevent heart attack trial (ALLHAT):

From the available data on Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), there was no significant difference for amlodipine-based therapy and chlorthalidone-based therapy in composite of fatal coronary heart disease or non-fatal myocardial infarction. In contrast, incidence of heart failure (component of a composite combined cardiovascular endpoint) showed to be significantly higher in amlodipine-based therapy compared to chlorthalidone-based therapy. However, there was no significant difference reported in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy.

Pharmacokinetics

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. 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.

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.

To achieve equimolar quantities and plasma concentrations of perindoprilat, a dosage of perindopril arginine 5 mg replaces perindopril-tert-butylamine 4 mg and a dosage of perindopril arginine 10 mg replaces perindopril-tert-butylamine 8 mg. Predclinical experiments found perindopril arginine and perindopril-tert-butylamine to be comparable in terms of their absorption, distribution, metabolism, and elimination characteristics. Their bioavailability was also found to be similar [Tejleko 2007].

Elderly, Heart Failure, Renal Failure

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

Hepatic impairment

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

Amlodipine:

Absorption, distribution, plasma protein binding

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

Biotransformation/elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme 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%.

Predclinical safety data

Perindopril:

In animal studies, perindopril shows no sign of embryotoxicity or teratogenicity. However, for angiotensin converting enzyme inhibitors class, animal studies in rodents and rabbits shows induced adverse effects on late foetal development, resulting in foetal death and congenital effects. In addition, renal lesions and increased of peri- and postnatal mortality also observed.

Amlodipine:

In the animal studies, amlodipine shows 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. Amlodipine shows no effect on the fertility of rats at doses up to 10 mg/kg/day. Animal studies in rats when dosed with human dose for 30 days shows decreased plasma follicle-stimulating hormone and testosterone, decreases in sperm density and number of mature spermatids and sertoli cells. Animal studies in rats and mice when dose with amlodipine for two years daily at 0.5,1.25 and 2.5mg/kg shows no evidence of carcinogenicity.

Mutagenicity studies shows Amlodipine does not effects gene or chromosome levels.

Instructions for Use and Handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

Storage Condition

Store in the original packaging in order to protect from light and moisture. Store below 30 °C.

Shelf Life

30 months

Dosage Forms and Packaging Available

Blister of PA-Aluminium-PVC/Aluminium foil in a carton box. Pack sizes of 30 tablets.

Name and Address of Manufacturer

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