

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

LISTRIL SM
(S-Amlodipine and Lisinopril Tablets)

COMPOSITION

Each uncoated tablet contains:

S-Amlodipine Besylate I.P. equivalent to S-Amlodipine.....2.5 mg

Lisinopril I.P. equivalent to Lisinopril Anhydrous..... 5 mg

Color: Lake of Sunset Yellow

DOSAGE FORM

Uncoated tablet

INDICATIONS

LISTRIL SM is indicated for use in the treatment of patients with mild to moderate hypertension.

POSOLOGY AND METHOD OF ADMINISTRATION

Lisinopril

Lisinopril should be administered orally in a single daily dose. As with all other medication taken once daily, Lisinopril should be taken at approximately the same time each day. The absorption of Lisinopril tablets is not affected by food.

The dose should be individualised according to patient profile and blood pressure.

Hypertension

Lisinopril may be used as monotherapy or in combination with other classes of antihypertensive therapy.

Starting dose

In patients with hypertension the usual recommended starting dose is 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and /or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment.

Maintenance dose

The usual effective maintenance dosage is 20 mg administered in a single daily dose. In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks on a certain dose level, the dose can be further increased. The maximum dose used in long-term, controlled clinical trials was 80 mg/day.

Diuretic-treated patients

Symptomatic hypotension may occur following initiation of therapy with lisinopril. This is more likely in patients who are being treated currently with diuretics. Caution is recommended

therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with lisinopril. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with lisinopril should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of lisinopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

Dosage adjustment in renal impairment

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in Table 1 below.

Table 1 Dosage adjustment in renal impairment

Creatinine Clearance (ml/min)	Starting Dose (mg/day)
Less than 10 ml/min (including patients on dialysis)	2.5 mg*
10-30 ml/min	2.5-5 mg
31-80 ml/min	5-10 mg

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response.

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Use in hypertensive paediatric patients aged 6–16 years

The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients \geq 50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients \geq 50 kg. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in paediatric patients.

In children with decreased renal function, a lower starting dose or increased dosing interval should be considered.

Heart failure

In patients with symptomatic heart failure, lisinopril should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. Lisinopril may be initiated at a starting dose of 2.5 mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of lisinopril should be increased:

- By increments of no greater than 10 mg
- At intervals of no less than 2 weeks
- To the highest dose tolerated by the patient up to a maximum of 35 mg once daily.

Dose adjustment should be based on the clinical response of individual patients.

Patients at high risk of symptomatic hypotension, e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous

diuretic therapy should have these conditions corrected, if possible, prior to therapy with lisinopril. Renal function and serum potassium should be monitored.

Paediatric population

There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Lisinopril is not recommended in children in other indications than hypertension.

Lisinopril is not recommended in children below the age of 6, or in children with severe renal impairment ($\text{GFR} < 30\text{ml/min/1.73m}^2$).

Older people

In clinical studies, there was no age-related change in the efficacy or safety profile of the drug. When advanced age is associated with decrease in renal function, however, the guidelines set out in Table 1 should be used to determine the starting dose of lisinopril. Thereafter, the dosage should be adjusted according to the blood pressure response.

Use in kidney transplant patients

There is no experience regarding the administration of lisinopril in patients with recent kidney transplantation. Treatment with lisinopril is therefore not recommended.

S-Amlodipine (Hypertension)

The recommended dose is 2.5 mg once daily taken with or without food, which may be increased to a maximum dose of 5 mg depending on the individual patient's response. No dosage adjustment is necessary for elderly patients or patients with renal disease. The half-life of S-Amlodipine is prolonged in patients with impaired liver function. S-Amlodipine should therefore be administered with caution in such patients.

FERTILITY, PREGNANCY AND LACTATION

Lisinopril

Pregnancy

<p>The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy.</p>

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 inhibitors therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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).

Should exposure to ACE inhibitors 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.

Breastfeeding

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

S-Amlodipine

Pregnancy

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. 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

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

Fertility

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

CONTRAINDICATIONS

Lisinopril

- Hypersensitivity to lisinopril, to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy.
- The concomitant use of lisinopril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²)

S-Amlodipine

Amlodipine is contraindicated in patients with:

- Hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients.
- 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.

WARNINGS AND PRECAUTIONS

Lisinopril

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving lisinopril, hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension. In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. 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 normal saline. 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 heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of lisinopril may be necessary.

Hypotension in acute myocardial infarction

Treatment with lisinopril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower, or those in cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg for more than 1 hour) then lisinopril should be withdrawn.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, lisinopril 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 function impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial lisinopril dosage should be adjusted according to the patient's creatinine clearance, and then as a function of the

patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin-converting enzyme 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. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of lisinopril therapy.

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 lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or lisinopril may be required.

In acute myocardial infarction, treatment with lisinopril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with lisinopril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of lisinopril.

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin-converting enzyme inhibitors, including lisinopril. This may occur at any time during therapy. In such cases, lisinopril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases 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.

Angiotensin-converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) 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.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoproteins (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.

Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure

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

Neutropenia/Agranulocytosis

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. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Lisinopril 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 lisinopril 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.

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.

Race

Angiotensin-converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, lisinopril may be less effective in lowering blood pressure in black patients 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, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

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.

Lithium

The combination of lithium and lisinopril is generally not recommended.

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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.

S-Amlodipine

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

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. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with impaired hepatic function

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

Elderly patients

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

Patients with 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.

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

DRUG INTERACTIONS

Lisinopril

Antihypertensive agents

When lisinopril is combined with other antihypertensive agents (e.g. glyceryl trinitrate and other nitrates, or other vasodilators), additive falls in blood pressure may occur.

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

Diuretics

When a diuretic is added to the therapy of a patient receiving lisinopril the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when lisinopril is added. The possibility of symptomatic hypotension with lisinopril can be minimised by discontinuing the diuretic prior to initiation of treatment with lisinopril.

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If lisinopril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥ 3 g/day

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. These effects are usually reversible. 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.

Gold

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Tricyclic antidepressants / Antipsychotics / Anaesthetics

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

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

Tissue Plasminogen Activators

Concomitant treatment with tissue plasminogen activators may increase the risk of angioedema.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

Lisinopril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

S-Amlodipine

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

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

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

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.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Cyclosporine

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

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

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

Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur. Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

UNDESIRABLE EFFECTS

Lisinopril

The following undesirable effects have been observed and reported during treatment with lisinopril and other ACE inhibitors with the following frequencies: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders	
rare:	decreases in haemoglobin, decreases in haematocrit
very rare:	bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia, lymphadenopathy, autoimmune disease.
Metabolism and nutrition disorders	
very rare:	hypoglycaemia.
Nervous system and psychiatric disorders	
common:	dizziness, headache
uncommon:	mood alterations, paraesthesia, vertigo, taste disturbance, sleep

	disturbances, hallucinations.
rare:	mental confusion, olfactory disturbance frequency
not known:	depressive symptoms, syncope.
Cardiac and vascular disorders	
common:	orthostatic effects (including hypotension)
uncommon:	myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients, palpitations, tachycardia, Raynaud's phenomenon.
Respiratory, thoracic and mediastinal disorders	
common:	cough
uncommon:	rhinitis
very rare:	bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia.
Gastrointestinal disorders	
common:	diarrhoea, vomiting
uncommon:	nausea, abdominal pain and indigestion
rare:	dry mouth
very rare:	pancreatitis, intestinal angioedema, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure.
Skin and subcutaneous tissue disorders	
uncommon:	rash, pruritus
rare:	urticaria, alopecia, psoriasis, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx.
very rare:	sweating, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma.
A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.	
Renal and urinary disorders	
common:	renal dysfunction
rare:	uraemia, acute renal failure
very rare:	oliguria/anuria.
Endocrine disorders	
rare:	syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Reproductive system and breast disorders	
uncommon:	impotence
rare:	gynaecomastia.

General disorders and administration site conditions	
uncommon:	fatigue, asthenia.
Investigations	
uncommon:	increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
rare:	increases in serum bilirubin, hyponatraemia.

Safety data from clinical studies suggest that lisinopril is generally well tolerated in hypertensive paediatric patients, and that the safety profile in this age group is comparable to that seen in adults.

Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very rare	Leukocytopenia, thrombocytopenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Insomnia, mood changes (including anxiety), depression
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paresthesia
	Very rare	Hypertonia, peripheral neuropathy
Eye disorders	Common	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)

	Very rare	Myocardial infarction
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth
	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Very rare	Hepatitis, jaundice, hepatic enzymes increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
	Very rare	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders	Common	Ankle swelling, muscle cramps
	Uncommon	Arthralgia, myalgia, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	Very common	Oedema
	Common	Fatigue, asthenia
	Uncommon	Chest pain, pain, malaise
Investigations	Uncommon	Weight increase, weight decrease

*mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

S-Amlodipine

Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very rare	Leukocytopenia, thrombocytopenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Insomnia, mood changes (including anxiety), depression
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paresthesia
	Very rare	Hypertonia, peripheral neuropathy
Eye disorders	Common	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare	Myocardial infarction
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth
	Very rare	Pancreatitis, gastritis, gingival

		hyperplasia
Hepatobiliary disorders	Very rare	Hepatitis, jaundice, hepatic enzymes increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
	Very rare	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders	Common	Ankle swelling, muscle cramps
	Uncommon	Arthralgia, myalgia, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	Very common	Oedema
	Common	Fatigue, asthenia
	Uncommon	Chest pain, pain, malaise
Investigations	Uncommon	Weight increase, weight decrease

*mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

OVERDOSE

Lisinopril

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

The recommended treatment of 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. If ingestion is recent, take measures aimed at eliminating Lisinopril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

S-Amlodipine

In humans experience with intentional overdose is limited.

Symptoms

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

Treatment

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

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

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

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

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Lisinopril

Mechanism of Action

Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin-converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

Pharmacodynamic effects

Whilst the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

Pharmacokinetic properties

Lisinopril is an orally active non-sulphydryl-containing ACE inhibitor.

Absorption

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25% with interpatient variability of 6-60% over the dose range studied (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure. Lisinopril absorption is not affected by the presence of food.

Distribution

Lisinopril does not appear to be bound to serum proteins other than to circulating angiotensin-converting enzyme (ACE). Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Elimination

Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine. On multiple dosing, lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril in healthy subjects is approximately 50 ml/min. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment

Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (about 30% as determined by urinary recovery), but an increase in exposure (approximately 50%) compared to healthy subjects due to decreased clearance.

Renal impairment

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. In mild to moderate renal impairment (creatinine clearance 30-80 ml/min), mean AUC was increased by 13% only, while a 4.5-fold increase in mean AUC was observed in severe renal impairment (creatinine clearance 5-30 ml/min).

Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55 ml/min.

Heart failure

Patients with heart failure have a greater exposure of lisinopril when compared to healthy subjects (an increase in AUC on average of 125%), but based on the urinary recovery of lisinopril, there is reduced absorption of approximately 16% compared to healthy subjects.

Paediatric population

The pharmacokinetic profile of lisinopril was studied in 29 paediatric hypertensive patients, aged between 6 and 16 years, with a GFR above 30 ml/min/1.73m². After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations of lisinopril occurred within 6 hours, and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults.

AUC and C_{max} values in children in this study were consistent with those observed in adults.

Older people

Older patients have higher blood levels and higher values for the area under the plasma concentration-time curve (increased approximately 60%) compared with younger subjects.

S-Amlodipine pharmacodynamics

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.

- 1) 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.
- 2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

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

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

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

Pharmacokinetics

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.

Use in 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%.

Use in the elderly

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

Use in children

A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

Preclinical safety data

Lisinopril

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Angiotensin-converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin-angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

S-Amlodipine

Reproductive toxicology

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

Impairment of fertility

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

Carcinogenesis, mutagenesis

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

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.
*Based on patient weight of 50 kg.

EXPIRY DATE:

Do not use later than expiry date.

STORAGE:

Store at a temperature not exceeding 25°C, protected from light and moisture.
Keep all medicines out of reach of children

PRESENTATION:

LISTRIL SM is available in strips of 10 tablets.

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