SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Skopryl® Combo 10 mg/5 mg tablets
Skopryl® Combo 20 mg/10 mg tablets
Skopryl® Combo 20 mg/5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Skopryl Combo 10 mg/5 mg tablets
Each tablet contains 10 mg of lisinopril (as dihydrate) and 5 mg of amlodipine (as besilate).

Skopryl Combo 20 mg/10 mg tablets
Each tablet contains 20 mg of lisinopril (as dihydrate) and 10 mg of amlodipine (as besilate).

Skopryl Combo 20 mg/5 mg tablets
Each tablet contains 20 mg of lisinopril (as dihydrate) and 5 mg of amlodipine (as besilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Skopryl Combo 10 mg/5 mg tablets
Round, white to off white, flat tablets with diameter of 8.00 ± 0.15 mm, with facet and break mark on one side, debossed with "L A" on the other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Skopryl Combo 20 mg/10 mg tablets
Round, white to off white, biconvex tablets with diameter of 11.00 ± 0.15 mm, with break mark on one side, debossed with "L A 2" on the other side.
The tablet can be divided into equal doses.

Skopryl Combo 20 mg/5 mg tablets
Round, white to off white, biconvex tablets with diameter of 11.00 ± 0.15 mm, with break mark on one side, debossed with "L A 1" on the other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

Skopryl Combo is indicated as substitution therapy of adult patients with blood pressure adequately controlled with lisinopril and amlodipine given concurrently at the same dose level.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet daily. The maximum daily dose is one tablet.
In general, fixed dose combination preparations are not suitable for initial therapy.

Skopryl Combo 10 mg/5 mg tablets is indicated only for patients in whom the optimal maintenance dose of lisinopril and amlodipine has been titrated to 10 mg and 5 mg.

Skopryl Combo 20 mg/10 mg tablets is indicated only for patients in whom the optimal maintenance dose of lisinopril and amlodipine has been titrated to 20 mg and 10 mg.

Skopryl Combo 20 mg/5 mg is indicated only for patients in whom the optimal maintenance dose of lisinopril and amlodipine has been titrated to 20 mg and 5 mg.

If dose adjustment becomes necessary, dose titration with the individual components can be considered.

Special populations

Renal impairment
To find the optimal starting dose and maintenance dose of patients with renal impairment, the patients should be individually titrated using the individual components of lisinopril and amlodipine.
Renal function, serum potassium and sodium levels should be monitored during therapy with Skopryl Combo. In the case of renal function deterioration, the use of Skopryl Combo should be discontinued and replaced by the individual components adequately adjusted. Amlodipine is not dialysable.

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 (see sections 4.4 and 5.2). To find the optimal starting dose and maintenance dose of patients with hepatic impairment, the patients should be individually titrated using the individual components of lisinopril and amlodipine.
The pharmacokinetics of amlodipine have not been studied in patients with severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Paediatric population (<18 years)
The safety and efficacy of Skopryl Combo in the paediatric population aged below 18 years have not been established.

Elderly (> 65 years)
Elderly patients should be treated with great caution.
In clinical studies, there was no age-related change in the efficacy or safety of amlodipine or lisinopril. To find the optimal maintenance dose for elderly patients they should be individually titrated using the individual components of lisinopril and amlodipine.

Method of administration
For oral use only.

Since food does not affect absorption, Skopryl Combo tablet may be taken irrespective of meals.

4.3 Contraindications

Related to lisinopril
- Hypersensitivity to lisinopril or to any other angiotensin converting enzyme (ACE) inhibitor
- A history of angioedema relating to previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimester of pregnancy (see sections 4.4 and 4.6)
- Concomitant use of Skopryl Combo tablet with medicinal products containing aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Skopryl Combo must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

Related to amlodipine
- Hypersensitivity to amlodipine or to any other dihydropyridine derivative
- Severe hypotension
- Shock (including cardiogenic shock)
- Obstruction in the outflow tract of the left ventricle (high grade aortic stenosis)
- Haemodynamically unstable heart failure after acute myocardial infarction.

Related to Skopryl Combo tablet
All of the above detailed contraindications related to the individual monocomponents are also relating to the fixed combination.
- Hypersensitivity to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

All of the warnings detailed below related to the individual monocomponents should also be considered for the Skopryl Combo fixed combination.

Related to 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, a low-salt diet, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). In patients with heart failure with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in 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 saline 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 heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with the use of 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 mmHg 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 mmHg or lower. Maintenance doses should be reduced to 5 mg or temporarily 2.5 mg if systolic blood pressure is 100 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg 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 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 signs of 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 hour. 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 ACE 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 discharging the patient. Even in those instances where swelling of only the tongue is involved, without respiratory failure, 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 initiated 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 (see section 4.3).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of lisinopril. Treatment with lisinopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Anaphylactoid reactions in haemodialysis patients
Anaphylactoid reaction has been reported in patients dialysed with high-flux (e.g. AN 69) membrane and treated concomitantly with an ACE inhibitor. In these patients, it is recommended to use a different type of dialysis membrane or a 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.

Desensitization
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 warned to report any sign of infection.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence showing that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and impaired renal function (including the risk of acute renal failure), therefore dual blockade with the combined use of RAAS ACE inhibitors, angiotensin II receptor blockers or aliskiren is not recommended (see sections 4.5 and 5.1).
If dual blockade treatment is deemed absolutely necessary, it should only be administered under the supervision of a specialist with frequent and close monitoring of renal function, electrolyte levels and blood pressure.
ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Ethnic differences
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.

Surgical intervention/anaesthesia
In patients undergoing a major surgical intervention 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.

Serum potassium
ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, hyperkalaemia may occur in patients with impaired renal function or in patients with diabetes and/or in patients taking concomitantly potassium supplements (including salt substitutes), potassium-sparing diuretics (e.g. spironolactone, triamterene, or amiloride), and other medicinal products that increase serum potassium (e.g. heparin, trimethoprim and co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists or angiotensin-receptor blockers. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

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

Lithium
Concomitant use of lithium and lisinopril is generally not recommended (see section 4.5).

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is 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 confirmed, treatment with ACE inhibitors should be stopped immediately. If needed, alternative therapy should be started (see sections 4.3 and 4.6).

Related to amlodipine

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to lisinopril

Antihypertensives
The antihypertensive effect of lisinopril may be potentiated by other concomitantly administered antihypertensive agents (e.g. glyceryl trinitrate and other nitrates, or other vasodilators).
Clinical study data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) with a combination of ACE inhibitors, angiotensin II receptor blockers or aliskiren is more likely to cause adverse reactions including hypotension, hyperkalaemia and impaired renal function (including acute renal failure) than use of a single agent acting on the RAAS (see sections 4.3, 4.4 and 5.1).

Medicines increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).
Concomitant use of ACE inhibitors with mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril), or tissue plasminogen activator or vildagliptin may lead to an increased risk of angioedema (see section 4.4).

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 (see section 4.4 and section 4.2).

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 lisinopril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium, particularly in patients with impaired renal function. Care should also be taken when lisinopril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as it is known to act as potassium-sparing diuretic like amiloride. Therefore, the combination of lisinopril 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 (see section 4.4).

If lisinopril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

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 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 (see section 4.4)

Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid at doses ≥3 g/day
Concomitant use of ACE-inhibitors and NSAIDs (e.g. acetylsalicylic acid used in an anti-inflammatory dosage regimen, COX-2 inhibitors and nonselective NSAIDs) may decrease the antihypertensive effect. Concomitant use of ACE-inhibitors and NSAIDs may increase the risk of deteriorating renal function – including acute renal failure – and elevated serum potassium levels, particularly in patients with pre-existing kidney dysfunction. These effects are usually reversible. Use of this combination requires caution, particularly in elderly patients. Accordingly, monitoring of renal function and adequate hydration of the patient is recommended at the start of treatment and periodically during treatment.

Gold
Nitritoid reactions (symptoms of vasodilatation, flushing, nausea, dizziness and hypotension, which can be very severe) following injections containing gold (for example sodium aurothiomalate) have been reported more frequently in patients receiving concomitant 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 (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effect 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.

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

Interactions related to amlodipine

Effects of other medicinal products on 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, which may result in a higher risk for hypotension. These pharmacokinetic changes may have greater clinical significance in the elderly. Clinical monitoring of

patients is recommended, and dose adjustment may thus be required.

Clarithromycin is an inhibitor of CYP3A4. There is a greater risk of hypotension in patients treated concomitantly with clarithromycin and amlodipine. Close observation of patients is recommended when amlodipine is administered concomitantly with clarithromycin.

CYP3A4 inducers
The concomitant use of known CYP3A4 inducers may alter the plasma concentration of amlodipine. Blood pressure should therefore be monitored and dose adjustment considered both during and after concomitant use, particularly with potent CYP3A4 inducers (e.g., rifampicin, St. John's wort [*Hypericum perforatum*]).

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 were observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, use of calcium channel blockers such as amlodipine should 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 blood levels of tacrolimus when used concomitantly with amlodipine, however the pharmacokinetic mechanism of this interaction is not yet fully known. In order to avoid tacrolimus toxicity in patients receiving amlodipine during tacrolimus therapy, the tacrolimus blood level should be monitored and the dose of tacrolimus adjusted if necessary.

mTOR (mammalian target of rapamycin) inhibitors
mTOR inhibitors such as sirolimus, temsirolimus and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. Concomitant administration of amlodipine with mTOR inhibitors may increase exposure to mTOR inhibitors.

Ciclosporin
No drug interaction studies have been conducted with ciclosporin and amlodipine on healthy volunteers or in other patient groups, except in kidney transplant patients in whom a variable increase (0–40% on average) in the trough concentration of ciclosporin was seen. The monitoring of ciclosporin levels should be considered in kidney transplant patients on amlodipine treatment, and the dose of ciclosporin should be decreased as needed.

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. The dose of simvastatin in patients on amlodipine should be limited to 20 mg daily.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of Skopryl Combo is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy.

No experience is available with the use of lisinopril and amlodipine in pregnant women from adequately controlled clinical studies. However, the use of both active substances during pregnancy is either not recommended or contraindicated (for substance-specific details, see below).

When pregnancy is confirmed, treatment with Skopryl Combo should be stopped immediately. If needed, alternative therapy should be started (see section 4.4).
Skopryl Combo treatment should not be initiated during pregnancy. Unless continued treatment with Skopryl Combo tablets is essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

Related to lisinopril

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is 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 confirmed, treatment with ACE inhibitors should be stopped immediately and if needed, alternative therapy should be started.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Related to amlodipine

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

Lactation
No information is available regarding the use of lisinopril during breast feeding.
Amlodipine is excreted in human milk. According to estimates, the dose absorbed by the infant is within the 3-7% interquartile range of the maternal dose, but is no more than 15%. The effects of amlodipine on the infant are not known.
Use of Skopryl Combo during breast-feeding is not recommended and alternative treatments with better established safety profiles during breast feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility
No experience is available with the effect of lisinopril and amlodipine on fertility from adequately controlled clinical studies.

Related to amlodipine

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

4.7 Effects on ability to drive and use machines

Related to lisinopril
When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

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

Based on the foregoing, Skopryl Combo may impact the ability to drive and use machines (especially during the early stage of treatment).

4.8 Undesirable effects

During a controlled clinical study (n=195), the incidence of adverse reactions was not higher in subjects receiving both active substances concomitantly than in patients on monotherapy. Adverse reactions were consistent with those reported previously with amlodipine and/or lisinopril. Adverse reactions were usually mild, transient and rarely warranted the discontinuation of treatment. The most common adverse reactions with the combination were headache (8%), cough (5%), and dizziness (3%).

Frequencies are defined as follows: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to <1/1,000), Very rare (< 1/10,000), Not known (frequency cannot be estimated from the available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

The following adverse drug reactions have been reported during the treatment with lisinopril and amlodipine independently:

System Organ Class	Frequency	ADRs with lisinopril	ADRs with amlodipine
Blood and Lymphatic System Disorders	Rare	Decrease in haemoglobin concentration, Decrease in haematocrit value	
	Very rare	Bone marrow depression, Agranulocytosis (see section 4.4), Leucopenia, Neutropenia, Thrombocytopenia, Haemolytic anaemia, Anaemia, Lymphadenopathies	Thrombocytopenia, Leucopenia
Immune System Disorders	Very rare	Autoimmune disorders	Allergic reactions
	Not known	Anaphylactic/anaphylactoid reaction	
Endocrine Disorders	Rare	Inappropriate antidiuretic hormone secretion	

		(SIADH)	
Metabolism and Nutrition Disorders	Very rare	Hypoglycaemia	Hyperglycaemia
Psychiatric Disorders	Uncommon	Mood changes, Sleep disturbances, Hallucinations	Insomnia, Mood changes (including anxiety), Depression
	Rare	Mental confusion	Confusion
	Not known	Depression	
Nervous System Disorders	Common	Dizziness, Headache	Drowsiness, Dizziness, Headache (especially at the beginning of the treatment)
	Uncommon	Vertigo, Paraesthesia, Dysgeusia	Syncope, Tremor, Dysgeusia, Hypaesthesia, Paraesthesia
	Rare	Parosmia (smell perception disorder)	
	Very rare		Hypertonia, Peripheral neuropathy
	Not known	Syncope	Extrapyramidal disorder
Eye Disorders	Common		Visual disturbances (including diplopia)
Ear and Labyrinth Disorders	Uncommon		Tinnitus
Cardiac Disorders	Common		Palpitations
	Uncommon	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4), Tachycardia, Palpitations	Arrhythmias (including bradycardia, ventricular tachycardia, atrial fibrillation)
	Very rare		Myocardial infarction
Vascular Disorders	Common	Orthostatic effects (including hypotension)	Flushing
	Uncommon	Cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), Raynaud's phenomenon	Hypotension
	Very rare		Vasculitis
Respiratory, Thoracic and Mediastinal Disorders	Common	Cough	Dyspnoea
	Uncommon	Rhinitis	Cough, Rhinitis
	Very rare	Bronchospasm, Allergic alveolitis/ Eosinophilic pneumonia, Sinusitis	
Gastrointestinal Disorders	Common	Diarrhoea,	Abdominal pain,

		Vomiting	Nausea, Dyspepsia, Altered bowel habit (diarrhoea and constipation)
	Uncommon	Abdominal pain, Nausea, Indigestion	Vomiting, Dry mouth
	Rare	Dry mouth	
	Very rare	Pancreatitis, Intestinal angioedema	Pancreatitis, Gastritis, Gingival hyperplasia
Hepatobiliary disorders	Very rare	Hepatitis – hepatocellular or cholestatic; Jaundice, Hepatic failure (see section 4.4)	Hepatitis, Jaundice, Hepatic enzyme increased**
Skin and Subcutaneous Tissue Disorders	Uncommon	Rash, Itching	Alopecia, Rash, Exanthema, Purpura, Skin discolouration, Hyperhidrosis, Itching, Urticaria
	Rare	Psoriasis, Urticaria, Alopecia Hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx (see section 4.4)	
	Very rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Pemphigus, Hyperhidrosis, Cutaneous pseudolymphoma*	Erythema multiforme, Angiooedema, Exfoliative dermatitis, Stevens-Johnson syndrome, Quincke's oedema, Photosensitivity
	Not known		Toxic epidermal necrolysis
Musculoskeletal and Connective Tissue Disorders	Common		Swelling of the ankles, Muscle cramps
	Uncommon		Joint pain, Muscle pain, Back pain
Renal and urinary disorders	Common	Renal dysfunction	
	Uncommon		Trouble passing urine, Nocturia, Increased urinary frequency

	Rare	Acute renal insufficiency, Uraemia	
	Very rare	Oliguria/anuria	
Reproductive system and breast disorders	Uncommon	Impotence	Impotence, Gynaecomastia
	Rare	Gynaecomastia	
General disorders and administration site conditions	Very common		Oedema
	Common		Fatigue, Asthenia
	Uncommon	Fatigue, Asthenia	Chest pain, Pain, Malaise
Investigations	Uncommon	Blood urea increased, Serum creatinine increased, Hyperkalaemia, Hepatic enzymes increased	Weight increased or Weight decreased
	Rare	Serum bilirubin increased, Hyponatraemia	

* A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.
** Mostly consistent with cholestasis

Safety data from clinical studies have shown that lisinopril is generally well tolerated in the paediatric population with hypertension and lisinopril has a similar safety profile to that seen in adults.

4.9 Overdose

No data are available on human overdosage with Skopryl Combo tablets.

Linked to lisinopril overdose
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 (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

Linked to amlodipine overdose
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, 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 beneficial 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.

Overdose with Skopryl Combo can result in excessive peripheral vasodilatation with marked hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Symptomatic treatment (placing the patient in a supine position, monitoring and when necessary, support of cardiac and respiratory function, blood pressure, fluid and electrolyte balance and creatinine concentrations) is recommended. In case of serious hypotension, the lower extremities should be elevated, and when intravenous administration of fluid does not elicit satisfactory response, supportive treatment with administration of peripheral vasopressor agents may be necessary, unless contraindicated. If available, treatment with angiotensin II infusion may also be considered. Intravenous administration of calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Lisinopril can be removed from the systemic circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided during dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and calcium channel blockers, lisinopril and amlodipine, ATC code: C09BB03

Skopryl Combo is a fixed dose combination containing the active substances lisinopril and amlodipine.

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.

Clinical efficacy and safety
The effect of lisinopril on mortality and morbidity in heart failure has been studied by comparing a high dose (32.5 mg or 35 mg once daily) with a low dose (2.5 mg or 5 mg once daily). In a study of 3164

patients, with a median follow up period of 46 months for surviving patients, high dose lisinopril produced a 12% risk reduction in the combined endpoint of all-cause mortality and all-cause hospitalisation (p = 0.002) and an 8% risk reduction in all-cause mortality and cardiovascular hospitalisation (p = 0.036) compared with low dose. Risk reductions for all-cause mortality (8%; p = 0.128) and cardiovascular mortality (10%; p = 0.073) were observed. In a post-hoc analysis, the number of hospitalisations for heart failure was reduced by 24% (p=0.002) in patients treated with high-dose lisinopril compared with low dose. Symptomatic benefits were similar in patients treated with high and low doses of lisinopril.

The results of the study showed that the overall adverse event profiles for patients treated with high or low dose lisinopril were similar in both nature and number. Predictable events resulting from ACE inhibition, such as hypotension or altered renal function, were manageable and rarely led to treatment withdrawal. Cough was less frequent in patients treated with high dose lisinopril compared with low dose.

In the GISSI-3 trial, which used a 2x2 factorial design to compare the effects of lisinopril and glyceryl trinitrate given alone or in combination for 6 weeks versus control in 19,394 patients who were administered the treatment within 24 hours of an acute myocardial infarction, lisinopril produced a statistically significant risk reduction in mortality of 11% versus control (2p=0.03). The risk reduction with glyceryl trinitrate was not significant but the combination of lisinopril and glyceryl trinitrate produced a significant risk reduction in mortality of 17% versus control (2p=0.02). In the sub-groups of elderly (age >70 years) and females, pre-defined as patients at high risk of mortality, significant benefit was observed for a combined endpoint of mortality and cardiac function. The combined endpoint for all patients, as well as the high-risk sub-groups, at 6 months also showed significant benefit for those treated with lisinopril or lisinopril plus glyceryl trinitrate for 6 weeks, indicating a prevention effect for lisinopril. As would be expected from any vasodilator treatment, increased incidences of hypotension and renal dysfunction were associated with lisinopril treatment but these were not associated with a proportional increase in mortality.

In a double-blind, randomised, multicentre trial which compared lisinopril with a calcium channel blocker in 335 hypertensive Type 2 diabetes mellitus subjects with incipient nephropathy characterised by microalbuminuria, lisinopril 10 mg to 20 mg administered once daily for 12 months, reduced systolic/diastolic blood pressure by 13/10 mmHg and urinary albumin excretion rate by 40%. When compared with the calcium channel blocker, which produced a similar reduction in blood pressure, those treated with lisinopril showed a significantly greater reduction in urinary albumin excretion rate, providing evidence that the ACE inhibitory action of lisinopril reduced microalbuminuria by a direct mechanism on renal tissues in addition to its blood pressure lowering effect.

Lisinopril treatment does not affect glycaemic control as shown by a lack of significant effect on levels of glycated haemoglobin (HbA_{1c}).

Agents impacting the renin-angiotensin system
The combined use of an ACE inhibitor and an angiotensin II receptor blocker was studied in two large-scale randomised controlled trials ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial] and VA NEPHRON-D [The Veterans Affairs Nephropathy in Diabetes]).
The ONTARGET trial was conducted on patients with a medical history of cardiovascular or cerebrovascular disease or type II diabetes mellitus associated with organ damage. The VA NEPHRON-D trial was conducted on patients with type II diabetes and diabetic nephropathy.
These studies did not show any significant benefits on renal and/or cardiovascular outcome and mortality, while the risk of hyperkalaemia, acute impaired renal function and/or hypotension increased compared to monotherapy. Based on the similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and angiotensin II receptor blockers.
ACE inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
The objective of the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal

Disease Endpoints) trial was to determine whether standard of care ACE inhibitor or angiotensin II receptor blocker treatment with aliskiren was beneficial in patients with type II diabetes and chronic kidney disease, or in patients with cardiovascular disease or both. The trial was terminated early as there was an increase in the risk of adverse reactions. The number of cardiovascular deaths and stroke was numerically higher in the aliskiren group compared to the placebo group, and significant adverse reactions and serious adverse events (hyperkalaemia, hypotension and kidney dysfunction) were also more frequent in the aliskiren group than in the placebo group.

Paediatric population
In a clinical study involving 115 paediatric patients with hypertension, aged 6-16 years, patients who weighed less than 50 kg received either 0.625 mg, 2.5 mg or 20 mg of lisinopril once a day, and patients who weighed 50 kg or more received either 1.25 mg, 5 mg or 40 mg of lisinopril once a day. At the end of 2 weeks, lisinopril administered once daily lowered trough blood pressure in a dose-dependent manner with a consistent antihypertensive efficacy demonstrated at doses greater than 1.25 mg.

This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mmHg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of lisinopril. The dose-dependent antihypertensive effect of lisinopril was consistent across several demographic subgroups: age, Tanner stage, gender, and race.

Amlodipine

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 antianginal effect of amlodipine is not entirely known, but amlodipine decreases total ischemic load through the following two mechanisms:

- Amlodipine dilates peripheral arterioles and thereby reduces total peripheral resistance (afterload) against which the heart works. As heart rate is unaffected, the smaller load on the heart decreases the energy utilisation and oxygen requirement of the myocardium.

- Amlodipine's mechanism of action probably includes the dilation of the main coronary arteries and coronary arterioles both in healthy and ischemic lesions. Increased blood vessel dilation increases oxygen supply to the myocardium in case of 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 pectoris, a once daily dose of amlodipine increases total exercise time and the time to the angina attack and time to 1 mm ST depression and decreases the frequency of angina attacks and the need for nitroglycerin tablets.

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

Cardiac failure
Haemodynamic studies and controlled clinical trials of patients with NYHA class II-IV heart failure that involved exercise have shown that amlodipine did not deteriorate the patients' clinical status based on exercise capacity, left ventricular ejection fraction and clinical symptoms.

In a placebo-controlled study (PRAISE) conducted on patients with NYHA class III-IV heart failure receiving digoxin, diuretics and an ACE inhibitor, ancillary use of amlodipine did not result in increased mortality or combined mortality and morbidity for the patients with heart failure.

In a long-term placebo-controlled follow-up trial with amlodipine (PRAISE-2) conducted on patients with NYHA class III-IV heart failure without clinical symptoms or diagnostic reports of ischemic heart disease, amlodipine alongside a fixed dose of ACE inhibitors, cardiac glycosides and diuretics did not have any impact on total cardiovascular mortality. In this same patient group amlodipine was associated with an increased number of reported cases of pulmonary oedema.

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
A randomized, double-blind, morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD (coronary heart disease) risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrolment) or documentation of other atherosclerotic CVD (cardiovascular disease) (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dl (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98; 95% CI: 0.90-1.07; p=0.65. Among the secondary endpoints, the incidence of heart failure (included in the composite cardiovascular endpoint) was significantly higher in the amlodipine group compared to the chlorthalidone group (10.2% vs 7.7%; RR: 1.38; 95% CI: 1.25-1.52; p < 0,001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.96; 95% CI: 0.89-1.02; p=0.20.

Paediatric population (6 years or older)
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced systolic blood pressure significantly more than placebo. The difference between the two doses was not statistically significant.
The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

5.2 Pharmacokinetic properties

Lisinopril

Lisinopril is an orally active non-sulfhydryl-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 inter-patient 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 ACE. Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Elimination
Lisinopril does not undergo metabolism and is excreted 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.

Pharmacokinetic characteristics in special populations

Hepatic impairment
Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (approximately 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 the elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically relevant only when the glomerular filtration rate is below 30 ml/min. In mild to moderate renal impairment (creatinine clearance 30 to 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 between 5 and 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 a 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/1.73m^2. 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.

Elderly
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.

Amlodipine

Absorption, distribution and plasma protein binding
After oral administration amlodipine is well absorbed, producing peak plasma concentrations between 6-12 hours post dose. Absolute bioavailability is 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 and elimination
The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Pharmacokinetic characteristics in special populations

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%.

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.

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

Fixed dose combination
No pharmacokinetic interactions have been described between the active substances of Skopryl Combo. Pharmacokinetic parameters (AUC, C_{max}, t_{max}, half-life) were not different from those observed after administration of the individual components separately.

The gastrointestinal absorption of the active substances of Skopryl Combo is not influenced by food.

5.3 Preclinical safety data

Preclinical studies have not been conducted with the combination of lisinopril and amlodipine.

Lisinopril
Non-clinical data reveal no special hazard of lisinopril for humans based on conventional studies of general pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
ACE inhibitors, as a class, have been shown to induce adverse effects on 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 rennin-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.

Amlodipine
Reproductive toxicity
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/day on a mg/m^2 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 (FSH) 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/day on a mg/m^2 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 level.

*Based on weight of 50 kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate
Mannitol
Pregelatinised maize starch
Sodium starch glycolate type A
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Skopryl Combo 10 mg/5 mg tablets:
Tablets are packed in PVC/PVDC/Aluminium foil blisters.
The card box contains 30 or 90 tablets in blisters and a package leaflet

Skopryl Combo 20 mg/ 10 mg tablets:
Tablets are packed in PVC/PVDC/Aluminium foil blisters.
The card box contains 30 or 90 tablets in blisters and a package leaflet

Skopryl Combo 20 mg/5 mg tablets:
Tablets are packed in PVC/PVDC/Aluminium foil blisters.
The card box contains 30 or 90 tablets in blisters and a package leaflet

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT