

ANNEX I

**LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL
PRODUCT, ROUTE OF ADMINISTRATION, APPLICANTS / MARKETING AUTHORISATION
HOLDERS IN THE MEMBER STATES**

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>(Invented) Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Bulgaria	Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary		Dironorm	10 mg/5 mg	tablets	oral use
Czech Republic		Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary	Lisonorm* ¹	10 mg/5 mg	tablets	oral use
Estonia		Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary.	Dironorm	10 mg/5 mg	tablets	oral use
Hungary	Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary.		Lisonorm	10 mg/5 mg	tablets	oral use
Latvia		Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary.	Dironorm	10 mg/5 mg	tablets	oral use
Lithuania		Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary.	Dironorm	10 mg/5 mg	tablets	oral use
Poland		Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary.	Dironorm	10 mg/5 mg	tablets	oral use

¹ Name approval pending

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>(Invented) Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
Romania		Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary.	Lisonorm 10mg/5mg	10 mg/5 mg	tablets	oral use
Slovak Republic		Gedeon Richter Plc. 1103 Budapest, Gyömrői út 19-21. Hungary.	Dironorm	10 mg/5 mg	tablets	oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS-PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF LISONORM AND ASSOCIATED NAMES (SEE ANNEX I)

Lisonorm is a new fixed-dose combination containing 10mg lisinopril (an ACE inhibitor) and 5mg amlodipine (a calcium antagonist), indicated for patients with blood pressure adequately controlled with lisinopril and amlodipine given concurrently at the same dose level. The applicant, Gideon Richter, sought a Marketing Authorisation in several member states (CZ, EE, LT, LV, PL, RO, and SK,) through the Mutual Recognition Procedure with Hungary acting as the reference member state. An Article 29 referral procedure was initiated due to concerns raised by the CZ and LV on the potential serious risk to public health regarding insufficient proof of bioequivalence since the Applicant did not use the originator's products (Aulin Gel) as reference treatments but used monocomponent-containing generics in the originally submitted bioequivalence study.

In line with the regulatory requirements (CHMP/EWP/191583/2005), a formal proof of bioequivalence, evidence of a wide therapeutic experience, and an adequately established benefit/risk ratio should be demonstrated for new fixed dose combination products claiming substitution indication. For Lisonorm (new lisinopril 10mg/ amlodipine 5mg combination), a positive benefit/risk ratio had not been established given that the initial bioequivalence study submitted was not conducted with the appropriate control, and that preliminary results of a new bioequivalence study (No.67289) did not allow a full assessment of the benefit risk ratio.

Therefore, the Applicant acknowledged the limitations arising from the product selection in the initial pivotal BE study and performed a study (Protocol No 67289) to investigate bioequivalence of LISONORM FORTE (fixed-combination of amlodipine 10 mg and lisinopril 20 mg), co-administration of NORVASC 10 mg (containing amlodipine 10 mg) and PRINIVIL 20 mg (containing lisinopril 20 mg), and LISONORM (fixed-combination of amlodipine 5 mg and lisinopril 10 mg) under fasting conditions.

Pharmacokinetic parameters were calculated for amlodipine and lisinopril by the means of Bioequiv 3.5 software using a model independent approach. The Applicant provided these pharmacokinetic results for amlodipine and lisinopril along with semi-logarithmic mean plasma concentration-time curves. The geometric mean ratios, 90% confidence intervals and corresponding intra-individual CVs for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for amlodipine and lisinopril were also presented.

Overall, the CHMP considered that the applicant had responded adequately by providing the results of an additional study, BES No.67289, and had demonstrated formal proof of bioequivalence. The overall design of the study was adequately pre-specified in the protocol and was considered acceptable. Subjects were selected by appropriate inclusion criteria and the regimen was standardized, excluding factors influencing pharmacokinetic interactions. The sampling interval and wash-out period were considered long enough and the statistical evaluation was also appropriate. LC-MS/MS methods were validated for analysis of both compounds, and the stability of the samples was documented over the period of sample storage.

Based on the data provided, bioequivalence for both amlodipine 10 mg and lisinopril 20 mg after administration of single oral doses of LISONORM FORTE, co-administration of NORVASC 10 mg and PRINIVIL 20 mg, or administration of LISONORM (fixed-combination of amlodipine 5 mg and lisinopril 10 mg) could be concluded. The 90% confidence intervals calculated for $AUC(0-t)$, $AUC(0-\infty)$ and C_{max} were within the range of 0.8-1.25 for both components (lisinopril and amlodipine).

With regards to safety, there were 3 drop-out subjects. A total of 96 post-dose adverse events were reported by 35 of the 48 subjects who received at least one dose of the study medication. As expected in this type of

medicinal product, headache was the most commonly reported adverse event. Additionally, there was a high incidence of QT prolongation observed in 16.7% subjects (n=8). The appearance of QT prolongation was similar in all 3 different treatment options, and there were no statistically significant differences between pre-dose and post-dose QTc values. In summary, there were no differences with respect to adverse events associated with the administration of amlodipine and lisinopril between the three investigated treatments, and no additional safety issues were raised by the results of the study.

GROUND

Whereas

- the Applicant has submitted a bioequivalence study, No. 67289, which shows that the test product induces comparable PK profiles for amlodipine and lisinopril in the fixed dose combination to those of the reference products (monocomponents).
- bioequivalence with the monocomponent products has been adequately demonstrated.
- the safety profile of the test product shows no differences with respect to adverse events associated with the administration of amlodipine and lisinopril compared to either reference treatments.

the CHMP has recommended the granting of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Lisonorm and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

ANNEX III
**SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lisonorm and associated names (see Annex I) 10/5 mg tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg lisinopril (as dihydrate) and 5 mg amlodipine (as besilate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White or off-white, round, flat, bevel-edged tablet with a score line on one side and with an engraving „A+L” on the reverse side. Diameter: about 8 mm.

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.

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

4.2 Posology and method of administration

The recommended dose is one tablet daily. The maximum daily dose is one tablet. Since food does not affect absorption, Lisonorm may be taken irrespective of meals.

Patients with 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. Lisonorm is indicated only for patients in whom the optimal maintenance dose of lisinopril and amlodipine has been titrated to 10 mg and 5 mg, respectively. Renal function, serum potassium and sodium levels should be monitored during therapy with Lisonorm. In the case of renal function deterioration, the use of Lisonorm should be discontinued and replaced by the individual components adequately adjusted.

Patients with hepatic impairment

The elimination of amlodipine may be prolonged in patients with impaired liver function. No precise dosage recommendations have been established for such cases and, therefore, this medicinal product should be administered with caution to patients with hepatic impairment.

Children and adolescents

Lisonorm is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

Elderly (> 65 years)

In clinical studies, there was no age-related change in the efficacy or safety profile of amlodipine or lisinopril. To find the optimal maintenance dose for elderly patients they should be individually titrated using the free combination of lisinopril and amlodipine. Lisonorm is indicated only for patients in whom the optimal maintenance dose of lisinopril and amlodipine has been titrated to 10 mg and 5 mg, respectively (see section 4.4).

4.3 Contraindications

- Hypersensitivity to lisinopril or to any other angiotensin converting enzyme (ACE) inhibitor.
- Hypersensitivity to amlodipine or to any other dihydropyridine derivatives.
- Hypersensitivity to any of the excipients.
- Severe hypotension.
- A history of angioedema relating to previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema (see section 4.4).
- Haemodynamically significant obstruction in the outflow tract of the left ventricle (aortic stenosis, hypertrophic cardiomyopathy), mitral stenosis or cardiogenic shock.
- Heart failure after acute myocardial infarction (during the first 28 days).
- Unstable angina pectoris (excluding Prinzmetal's angina).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Symptomatic hypotension

Substantial decrease in blood pressure and hence symptomatic hypotension can occur in patients with volume and/or sodium depletion resulting from diuretic therapy, fluid loss of other origin such as excessive diaphoresis, prolonged vomiting and/or diarrhoea (see section 4.2). If hypotension occurs, the patient should be placed in a supine position and intravenous fluid replacement (intravenous infusion of physiologic saline) should be administered if necessary. Preferably, sodium and/or volume depletion should be corrected before treatment with Lisonorm is started. The magnitude of antihypertensive effect should be closely monitored after administering the initial dose.

Aortic and mitral stenosis, obstructive hypertrophic cardiomyopathy

As with all vasodilators, Lisonorm should be administered with caution to patients with obstruction in the outflow tract of the left ventricle and with stenosis of mitral valve.

Renal function impairment

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 angiotensin converting enzyme inhibitors has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment.

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. To find the optimal maintenance dose of patients with renal impairment, the patients should individually be titrated using the individual components of lisinopril and amlodipine, with close monitoring of renal function. Lisonorm is indicated only for patients with titrated optimal maintenance dose of lisinopril and amlodipine of 10 mg and 5 mg, respectively.

In the case of renal function deterioration, Lisonorm should be withdrawn and replaced by the therapy with individual components adequately adjusted. Dose reduction and/or discontinuation of the diuretic may also be required.

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including lisinopril. In such cases, Lisonorm should be discontinued immediately and the patient kept under close medical supervision until complete and sustained resolution of symptoms has occurred.

Where swelling is confined to the face, lips and extremities, it usually resolves spontaneously; nevertheless, antihistamines may be useful in relieving symptoms.

Angioedema accompanied by laryngeal oedema is potentially fatal. If the oedematous swelling involves the tongue, glottis or larynx, or it is likely to cause airway obstruction; emergency treatment should be initiated promptly. Appropriate measures include the subcutaneous administration of 0.3-0.5 mg adrenaline epinephrine or the slow intravenous administration of 0.1 mg adrenaline, followed by glucocorticoids and antihistamines, with simultaneous monitoring of vital functions.

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

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

Anaphylactoid reactions in haemodialysis patients

Anaphylactic shock has been reported in patients dialysed with polyacrylonitrile (e.g. AN 69) membrane and treated concomitantly with an ACE inhibitor, therefore, this combination must be avoided. 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.

Bee/wasp venom desensitization

Occasionally, patients receiving ACE inhibitors during desensitization with *Hymenoptera* (e.g. wasp, bee) venom have experienced anaphylactoid reactions. These life-threatening reactions can be avoided by temporary withdrawal of ACE inhibitor therapy.

Hepatotoxicity

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

Hepatic impairment

The half-life of amlodipine is prolonged in patients with impaired liver function. Since no dose recommendations have been established, this medicinal product should therefore be administered with caution, weighing individually the expected benefits and potential risks of the treatment.

Haematological toxicity

Very rarely, neutropenia, agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors (see section 4.8). 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. Lisinorm 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 Lisinorm 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.

Cough

Commonly, 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/general 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, probably as a consequence of this mechanism, it can be corrected by volume expansion

Elderly

When advanced age is associated with decrease in renal function Lisinorm dose adjustments for patients with renal impairment apply (see section 4.2).

Hyperkalaemia

Elevations in potassium serum levels have been observed in some patients treated with ACE inhibitors. Patients at risk for the development of hyperkalaemia include those with renal impairment, diabetes mellitus, acute cardiac decompensation, dehydration, metabolic acidosis, or concomitant use of potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or any medicinal products associated with increases in potassium serum levels (e.g. heparin). If concomitant use of the abovementioned substances is needed, regular monitoring of potassium serum levels is recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to lisinopril

Substances affecting potassium levels: Potassium-sparing diuretics (e.g. spironolactone, amiloride, and triamterene), potassium supplements, or potassium-containing salt substitutes and other substances that may increase potassium levels (e.g. heparin) can lead to hyperkalaemia in combination with ACE inhibitors, particularly in patients with renal impairment and other pre-existing conditions (see section 4.4). If a medicinal product that affects potassium levels is to be prescribed in combination with lisinopril, monitoring of potassium serum levels is advised. Therefore, concomitant administration should be carefully considered and only undertaken with **increased caution and regular monitoring** of both serum potassium levels and renal function.

Diuretics: When a diuretic is added to the therapy of a patient receiving Lisinorm the antihypertensive effect is usually additive (see section 4.4). Lisinopril mitigates the kaliuretic effect of diuretics.

Other antihypertensives: Concomitant use of these agents may increase the hypotensive effects of Lisinorm. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

Tricyclic antidepressants/antipsychotics/anaesthetics/narcotics: Concomitant use with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Alcohol enhances the hypotensive effect.

Allopurinol, procainamide, cytostatics or immunosuppressive agents (systemic corticosteroids) may lead to an increased risk of leukopenia when administered concomitantly with ACE inhibitors.

Antacids decrease the bioavailability of the concomitant use of ACE inhibitors.

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored to confirm that the desired effect is being obtained.

Antidiabetics: Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (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.

Non-steroidal anti-inflammatory drugs (NSAIDs): Chronic administration of NSAIDs, including high-dosed acetylsalicylic acid ≥ 3 g/day, may reduce the antihypertensive effect of an ACE inhibitor.

NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Lithium: Lithium elimination may be reduced during concomitant use of ACE inhibitor and therefore, serum lithium levels should be monitored.

Interactions related to amlodipine

CYP3A4 inhibitors: A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded. Caution is required with concomitant use.

CYP3A4 inducers: Co-administration with anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone), rifampicin, herbal preparations containing St. John's wort/*Hypericum perforatum*) may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal. Caution is required with concomitant use.

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

4.6 Pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy and they are contraindicated in the second and third trimester.

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. ACE inhibitors therapy exposure 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).

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect (see section 5.3). There is, however, no clinical experience with the use of amlodipine in pregnancy. Accordingly, amlodipine is contraindicated during pregnancy.

No experience is available with the use of Lisonorm in pregnant women from adequately controlled clinical studies. Consequently, Lisonorm is contraindicated in pregnancy (see section 4.3).

When pregnancy is diagnosed, treatment with Lisonorm should be stopped immediately. Patients planning pregnancy Lisonorm should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

Lactation

Lisonorm is not recommended for breast-feeding mothers, as lisinopril may be excreted in human milk (see section 4.3). It is not known whether amlodipine is excreted in human milk.

4.7 Effects on ability to drive and use machines

Lisonorm may influence the ability to drive and operate machines (particularly during the initial period 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 with Lisonorm. The most common adverse reactions with the combination were headache (8%), cough (5%), and dizziness (3%).

In controlled clinical trials, the following adverse reactions were reported in $\geq 1\%$ of patients with either concomitantly administered amlodipine plus lisinopril or with amlodipine and lisinopril monotherapies (see Table below):

System Organ Class	Adverse reaction	Lisonorm (n=64)	Amlodipine (n=64)	Lisinopril (n=68)
Nervous system disorders	Dizziness	3%	1.5%	4.4%
	Headache	8%	6%	8.8%
Cardiac disorders	Palpitation	1.5%	4.6%	
Respiratory, thoracic and mediastinal disorders	Cough	5%	3%	
Gastrointestinal disorders	Nausea		1.5%	
Skin and subcutaneous tissue disorders	Pruritus	1.5%		

Frequencies are defined as follows: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following adverse drug reactions (ADRs) 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	Very rare	Bone marrow depression, Agranulocytosis, Leucopenia, Neutropenia, Thrombocytopenia, Haemolytic anaemia Anaemia, Lymphadenopathies	Thrombocytopenia
Immune system disorders	Very rare	Autoimmune disorders	Hypersensitivity
Metabolism and nutrition disorders	Very rare	Hypoglycaemia	Hyperglycaemia
Psychiatric disorders	Uncommon	Mood altered, Sleep disturbances	Insomnia, Mood altered
	Rare	Mental disorders	
Nervous system disorders	Common	Dizziness, Headache	Somnolence, Dizziness, Headache
	Uncommon	Vertigo, Paraesthesia, Taste disturbance	Syncope, Tremor, Taste perversion, Hypoaesthesia, Paraesthesia
	Very rare		Peripheral neuropathy
Eye disorders	Uncommon		Visual disturbances
Ear and labyrinth disorders	Uncommon		Tinnitus
Cardiac disorders	Common	Myocardial infarction (see section 4.4), Tachycardia, Palpitations,	Palpitations
	Uncommon		Myocardial infarction, Ventricular tachycardia, Atrial fibrillation, Arrhythmia
	Very rare		
Vascular disorders	Common	Orthostatic hypotension	Flushing
	Uncommon	Cerebrovascular accident (see section 4.4), Raynaud's phenomenon	Hypotension
	Very rare		Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Cough	Dyspnoea, Rhinitis
	Uncommon	Rhinitis	

System Organ Class	Frequency	ADRs with lisinopril	ADRs with amlodipine
	Very rare	Bronchospasm, Allergic alveolitis/Eosinophilic pneumonia, Sinusitis	Cough
Gastrointestinal disorders	Common	Diarrhoea, Vomiting	Abdominal pain, Nausea
	Uncommon	Abdominal pain, Nausea, Indigestion	Vomiting, Dyspepsia, Altered bowel habits, Dry mouth
	Rare	Dry mouth	
	Very rare	Pancreatitis, Intestinal angioedema	Pancreatitis, Gastritis, Gingival hyperplasia
Hepatobiliary disorders	Very rare	Hepatic failure, Hepatitis, Cholestatic jaundice, (see section 4.4)	Hepatitis, Jaundice, Cholestasis
Skin and subcutaneous tissue disorders	Uncommon	Hypersensitivity/angioedema of the face, extremities, lips, tongue, glottis and/or larynx (see section 4.4), Rash, Pruritus	Alopecia, Rash, Purpura, Skin discolouration, Diaphoresis, Pruritus
	Rare	Psoriasis, Urticaria, Alopecia	
	Very rare	Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, Erythema multiforme. Pemphigus, Diaphoresis. A syndrome has been reported that may include one or more of the following symptoms: fever, vasculitis, myalgia, arthralgia/arthritis, positive ANA, elevated ESR value, eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations.	Erythema multiforme, Angioedema, Urticaria
Musculoskeletal and connective tissue disorders	Uncommon		Arthralgia, Myalgia, Muscle cramps, Back pain
Renal and urinary disorders	Common	Renal dysfunction	
	Uncommon		Micturition disorder, Nocturia, Increased urinary frequency
	Rare	Acute renal failure, Uraemia	

System Organ Class	Frequency	ADRs with lisinopril	ADRs with amlodipine
	Very rare	Oliguria/Anuria	
Reproductive system and breast disorders	Uncommon	Impotence	Impotence, Gynaecomastia
	Rare	Gynaecomastia	
General disorders and administration site conditions	Common		Oedema, Fatigue
	Uncommon	Fatigue, Asthenia	Chest pain, Pain, Malaise, Asthenia
Investigations	Uncommon	Blood urea increased, Serum creatinine increased, Hyperkalaemia, Hepatic enzymes increased	Weight increase, Weight decrease
	Rare	Haemoglobin decreased, Haematocrit decreased, Serum bilirubin increased, Hyponatraemia	
	Very rare		

4.9 Overdose

Overdose 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 function, blood pressure, fluid and electrolyte balance) is recommended. In case of serious hypotension, the lower extremities should be elevated, and when intravenous administration of fluid does not elicit sufficient response, supportive treatment added-on 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.

Since amlodipine is slowly absorbed, gastric lavage can be useful in some cases.

Lisinopril can be removed from the systemic circulation by haemodialysis. Amlodipine, however, is highly protein-bound and, therefore, dialysis is not likely to be of benefit (see section 4.4.)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and calcium channel blockers, ATC code: not yet assigned.

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

Lisinopril

Lisinopril is an angiotensin converting enzyme (ACE) inhibitor, which results in reduction of plasma angiotensin II and consequently aldosterone levels and elevates those of vasodilatory bradykinin. It reduces peripheral vascular resistance and systemic blood pressure. These changes may be accompanied by an increase in cardiac output at unchanged heart frequency, as well as an increase in renal blood flow. In hyperglycaemic patients, lisinopril contributes to the restoration of impaired endothelial function.

The antihypertensive effect of lisinopril usually ensues 1 hour after administration and peaks after 6 hours. Its duration of action is 24 hours – also depending on dose. The antihypertensive efficacy of lisinopril is also maintained on the long term. Abrupt discontinuation of lisinopril treatment is not associated with any substantial rebound effect (blood pressure elevation).

Although its primary effect is mediated by the renin-angiotensin-aldosterone system, lisinopril is also effective in hypertensive patients with low plasma renin activity. In addition to its direct blood pressure lowering effect, lisinopril mitigates albuminuria by modifying the haemodynamic conditions and tissue structure in the renal glomeruli. In controlled clinical trials conducted in diabetic patients, no changes of blood glucose level and no increase in the incidence of hypoglycaemia were ascertained.

Amlodipine

Amlodipine is a dihydropyridine-type calcium channel blocker. It inhibits the influx of calcium into myocardial and vascular smooth muscle cells through the inhibition of slow calcium ion channels of the cell membranes. Amlodipine reduces the tone of smooth muscle in arterioles and hence the peripheral vascular resistance which lowers systemic blood pressure. Amlodipine exerts antianginal effect through the dilation of peripheral arterioles as well as through reduction of cardiac afterload, without resulting in reflex tachycardia, and accordingly, energy consumption and oxygen demand of cardiac muscle decrease. Amlodipine may dilate coronary vessels (arteries and arterioles); it improves oxygen supply to the myocardium both in intact and in ischaemic regions.

Once daily dosing of amlodipine reduces the blood pressure of hypertensive patients both in the supine and standing position throughout the 24-hour interval. Due to the slow onset of action, acute hypotension does not occur.

Calcium channel blocking activity, for example elicits direct arterial dilation accompanied by sodium and water retention. Compensatory activation of the renin-angiotensin-aldosterone system (RAAS) should be expected and therefore, counter-regulatory mechanisms activated by ACE inhibitors may contribute to the restoration of physiological responses to increased salt intake.

5.2 Pharmacokinetic properties

Lisinopril

Following oral administration, peak plasma concentrations occur after approximately 6 hours; its bioavailability is 29 %. Lisinopril does not bind to plasma proteins other than ACE; it is not metabolized in the organism and is excreted unchanged in the urine. The effective half-life of lisinopril is 12.6 hours. The major elimination of non protein-bound fraction is accompanied by that of ACE-bound lisinopril at a slower rate, and this can result in prolonged antihypertensive action.

The elimination of lisinopril is prolonged in renal impairment and therefore, dose reduction may be necessary (see section 4.2).

Lisinopril can be removed from the plasma by dialysis.

Amlodipine

Amlodipine is slowly and almost completely absorbed from the gastrointestinal tract following oral administration. Its absorption is unaffected by the consumption of food. Peak plasma concentration (C_{max}) occurs 6 to 10 hours after dosing. The bioavailability of amlodipine is 64 to 80 %; its volume of distribution is approximately 20 l/kg. In the systemic circulation 95 to 98 % of amlodipine is bound to plasma protein. Amlodipine is extensively metabolized by the liver to inactive metabolites with 10 % of the unchanged parent compound and 60 % of metabolites are excreted in the urine. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels are reached after 7 to 8 days of consecutive daily dosing. Amlodipine is transformed into inactive metabolites in the liver primarily, with 10 % of the unchanged parent compound excreted in the urine. Amlodipine cannot be removed from the plasma by dialysis.

The time to reach peak plasma concentrations (t_{max}) of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be lower with resulting increase in AUC and elimination half-life in the elderly. Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated and therefore, normal dose is recommended for older people.

The half-life of amlodipine is prolonged in patients with hepatic impairment.

In patients with renal impairment, changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Fixed dose combination

No pharmacokinetic interactions have been described between the active substances of Lisonorm . 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 Lisonorm is not influenced by food.

5.3 Preclinical safety data

Lisinopril

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Fertility was not affected in female and male rats in doses up to 300 mg/kg (33 times the maximum recommended human daily dose when compared on a body surface area). No teratogenic effects of lisinopril were seen in mice, rats and rabbits given doses that were 55 times, 33 times and 0.15 times, respectively, the maximum recommended human daily dose.

Amlodipine

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Teratogenic or other embryo/fetotoxic effects were not found in rats and rabbits given up to 10 mg/kg amlodipine (8 times and 23 times, respectively, the maximum recommended human daily dose of 10 mg on a mg/m^2 basis) during gestation. Amlodipine at this dose level prolonged both the gestation and labour duration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C

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

6.5 Nature and contents of container

30 tablets in white, opaque PVC/PE/PVDC/Aluminium blisters.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Folded Carton

1. NAME OF THE MEDICINAL PRODUCT

Lisonorm (see Annex I) 10/5 mg tablets
[See Annex I - To be completed nationally]
lisinopril/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg lisinopril (as dihydrate) and 5 mg amlodipine (as besilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in the original package in order to protect from light and moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]
[See Annex I - To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lisonorm 10/5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT

Lisonorm (see Annex I) 10/5 mg tablets
[See Annex I - To be completed nationally]
lisinopril/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Batch

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Lisonorm and associated names (see Annex I) 10 mg/5mg tablets
[See Annex I - To be completed nationally]
Lisinopril/Amlodipine

Read all of this leaflet carefully before you start taking this medicine.

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

In this leaflet:

1. What Lisonorm is and what it is used for
2. Before you take Lisonorm
3. How to take Lisonorm
4. Possible side effects
5. How to store Lisonorm
6. Further information

1. WHAT LISONORM IS AND WHAT IT IS USED FOR

Lisonorm tablet is a combination product of amlodipine, which belongs to a group of medicines called calcium channel blockers, and lisinopril, which belongs to a group of medicines called angiotensin-converting enzyme (ACE) inhibitors. Lisonorm is used to treat hypertension (high blood pressure). You might not have any symptoms from your too high blood pressure, but it may increase the risk of certain complications (such as stroke or heart attack), if you do not take your antihypertensive medicine regularly.

2. BEFORE YOU TAKE LISONORM

Do not take Lisonorm

You must not take this medicine:

- if you are allergic (hypersensitive) to the active substances or any of the other ingredients of Lisonorm
- if you are allergic to other ACE inhibitors (such as enalapril, captopril and ramipril) or other calcium channel blockers (such as nifedipine, felodipine or nimodipine)
- if you have had an angioedema (symptoms such as itching, nettle rash, wheezing and swelling of the hands, throat, mouth or eyelids), related or not to treatment with an ACE-inhibitor
- if your blood pressure is too low (severe hypotension)
- if you have a narrowing of the aorta (aortic stenosis), of a heart valve (mitral stenosis), an increase in the thickness of the heart muscle (hypertrophic cardiomyopathy) or cardiogenic shock (not enough blood supply to your tissues)
- if you have unstable angina (except Prinzmetal's angina)
- if you have suffered a heart attack (myocardial infarction) within the last 28 days
- if you are pregnant or think you may be pregnant
- if you are breast-feeding

Take special care with LISONORM

You should check with your doctor before taking this medicine if you:

- have heart problems

- have kidney problems
- have liver problems
- are under dialysis
- are about to have a treatment called LDL apheresis for removal of cholesterol
- are older than 65 years
- if you are on a low-salt diet and you use potassium containing salt substitutes or supplements
- have diarrhoea or vomiting
- desensitisation treatment to reduce allergy to bee or wasp stings
- are taking any medicines listed below

Taking other medicines

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

Potassium-sparing diuretics (such as spironolactone, amiloride, triamterene, used to reduce fluid retention) may only be taken together with Lisonorm under close medical supervision.

Special caution is necessary when Lisonorm is taken together with the following medicines:

- *diuretics (used to reduce fluid retention)*
- *other medicines used to lower blood pressure (antihypertensives)*
- *non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid (used to treat for arthritis, muscle pains, headache, inflammation, fever)*
- *lithium, antipsychotics, used to treat mental disorders*
- *insulin and oral antidiabetics*
- *autonomous nervous system stimulants (sympathomimetics), such as ephedrine, phenylephrine, xylometazoline and salbutamol, used to treat congestion, cough, cold and asthma.*
- *immunosuppressants, used to prevent transplant rejection*
- *allupurinol, used to treat gout*
- *narcotics, morphine and related drugs used to treat severe pain*
- *anticancer drugs*
- *antacids, used to treat stomach acidity*
- *anaesthetics, used in surgery or some dental procedures. Tell your doctor or dentist that you are taking Lisonorm before you are given a local or general anaesthetic, given the risk of short-term drop in blood pressure*
- *anticonvulsants (such as carbamazepine, phenobarbital and phenytoin), used to treat epilepsy*
- *medicines used to treat bacterial (rifampicin), HIV (ritonavir) or fungal infections (ketoconazole).*
- *herbal preparations containing St. John's wort (*Hypericum perforatum*)*

Taking Lisonorm with food and drink

Lisonorm can be taken with or without food, but alcohol should be avoided during treatment.

Pregnancy and breast-feeding

*Lisonorm **must not** be taken during pregnancy and breast-feeding.*

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

Driving and using machines

Lisonorm can affect your ability to drive and use machinery safely.

3. HOW TO TAKE LISONORM

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

If you have the impression that the effect of Lisonorm is too strong or too weak, talk to your doctor or pharmacist.

If you take more Lisonorm than you should

Contact your doctor immediately or go to the casualty department of the nearest hospital.

Overdose is likely to result in very low blood pressure, which has to be closely monitored, and if characteristic symptoms such as dizziness and headache occur, you should be placed lying down with the face up. Your doctor will take further measures.

If you forget to take Lisonorm

Do not take a double dose to make up for a forgotten tablet, to avoid the risk of overdose. Take your next dose at the usual time.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Lisonorm can cause side effects, although not everybody gets them.

Frequencies are defined as follows:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Common side effects in a clinical trial with Lisonorm tablets were: headache, cough, dizziness, palpitations (a quicker or irregular heart beat), and pruritus.

Allergic (hypersensitivity) reactions may occur with the use of Lisonorm . You must stop taking Lisonorm and seek medical attention immediately if you develop any of the following symptoms of *angioedema*:

- difficulty in breathing with or without swelling of the face, lips, tongue and/or throat.
- swelling of the face, lips, tongue and/or throat which may cause difficulty in swallowing.
- severe itching of the skin (with raised lumps).

Additional side effects that have been reported with either amlodipine or lisinopril alone (the two active substances), and may also occur with Lisonorm are the following:

Amlodipine

Common side effects

Headache, oedema (for example ankle swelling), feeling tired, sleepiness, feeling sick, dizziness, abdominal pain, palpitations (a quicker or irregular heart beat), nausea, flushing.

Tell your doctor if these effects cause you any problems or if they last for more than one week.

Uncommon side effects

Skin rash, itchy skin, indigestion, shortness of breath, muscle cramps, altered bowel habit, muscle or joint pain, back pain, chest pain, mood changes, tremor, visual disturbances, tinnitus, hypotension, difficulty in breathing, taste perversion, runny nose, increased need to urinate, dry mouth, thirst, loss of pain sensation, increased sweating, fainting, weakness, enlargement of breasts in men, impotence, weight increase, weight decrease.

Very rare side effects

Allergic reactions, abnormal liver function test, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), elevation of blood glucose, heart attack (myocardial infarction), irregular heartbeat (arrhythmia), cough, severe skin reactions, swelling or soreness of the gums, red patches on skin.

Lisinopril

Common side effects

Headache, dizziness or light-headedness especially when standing up quickly, diarrhoea, cough, vomiting, reduction of urine volume.

Uncommon side effects

Mood changes, angioedema (hypersensitivity reaction with sudden swelling of the lips, face and neck, and occasionally of the feet and hands; higher rate of angioedema in black patients than in non-black patients), change of colour (pale blue followed by redness) and/or numbness or tingling in the fingers or toes (Raynaud's phenomenon), changes in the way things taste, fatigue, feeling sleepy or difficulty in going to sleep, strange dreams, rapid heartbeat, runny nose, nausea, stomach pain or indigestion, skin rash, itching, impotence, tiredness, muscle weakness).

Rare side effects

Confusion, acute kidney problems, dry mouth, hair loss, psoriasis, enlargement of breasts in men. Deterioration of blood-picture: decrease of red blood cells, of platelets (thrombocytopenia), of white blood cells (neutropenia, leucopenia, agranulocytosis). This may result in prolonged bleeding, tiredness, weakness, disease of the lymph node, autoimmune disease (in which the body attacks itself). Infections are more likely.

Very rare side effects

Decrease of blood glucose (hypoglycaemia), sinus pain wheezing, inflammation of the lungs, yellow skin and/or eyes (jaundice), inflammation of the liver or pancreas, severe skin disorders (symptoms of which include redness, blistering and peeling), sweating.

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

5. HOW TO STORE LISONORM

Store below 25°C.

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

Keep out of the reach and sight of children.

Do not use Lisonorm tablets after the expiry date which is stated on the blisters and the carton after 'Exp'. The expiry date refers to the last day of that month.

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

6. FURTHER INFORMATION

What LISONORM contains

- The active substances are lisinopril and amlodipine. Each tablet contains 10 mg lisinopril (as dihydrate) and 5 mg amlodipine (as besilate).
- The other ingredients are cellulose microcrystalline, sodium starch glycolate (type A) and magnesium stearate.

What LISONORM looks like and contents of the pack

The tablets are white or almost white, round, flat, bevel-edged tablet with a score line on one side and with an engraving „A+L” on the reverse side. Diameter: about 8 mm

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Packs contain 30 tablets in white, opaque PVC/PE/PVDC-aluminium blisters.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

{Name of the Member State} {Name of the medicinal product}

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]