

**LISINOPRIL 2.5MG TABLETS
(LISINOPRIL DIHYDRATE)
PL 20092/0008**

**LISINOPRIL 5MG TABLETS
(LISINOPRIL DIHYDRATE)
PL 20092/0009**

**LISINOPRIL 10MG TABLETS
(LISINOPRIL DIHYDRATE)
PL 20092/0010**

**LISINOPRIL 20MG TABLETS
(LISINOPRIL DIHYDRATE)
PL 20092/0011**

UK Public Assessment Report

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LISINOPRIL 2.5MG, 5MG, 10MG & 20MG TABLETS
(LISINOPRIL DIHYDRATE)
PL 20092/0008, 0009, 0010 & 0011

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Lupin (Europe) Limited Marketing Authorisations (licences) for the medicinal products Lisinopril 2.5mg Tablets (PL 20092/0008), Lisinopril 5mg Tablets (PL 20092/0009), Lisinopril 10mg Tablets (PL 20092/0010), and Lisinopril 20mg Tablets (PL 20092/0011) on 20th June 2007. These are prescription-only medicines (POM) used for the treatment of high blood pressure, heart failure, kidney problems related to diabetes and high blood pressure, and after a heart attack to slow down weakening of your heart.

Lisinopril Tablets contain the active ingredient lisinopril. It acts by widening your blood vessels, which helps reduce your blood pressure and makes it easier for your heart to pump blood to all parts of the body.

The test products were considered to be the same as the reference products Zestril Tablets 2.5mg, 5mg, 10mg and 20mg respectively (PL 17901/0060, 0061, 0062 & 0063, AstraZeneca UK Limited) based on the data submitted by Lupin (Europe) Limited.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Lisinopril 2.5mg, 5mg, 10mg and 20mg Tablets outweigh the risk; hence Marketing Authorisations have been granted.

**LISINOPRIL 2.5MG, 5MG, 10MG & 20MG TABLETS
(LISINOPRIL DIHYDRATE)
PL 20092/0008, 0009, 0010 & 0011**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Lupin (Europe) Limited Marketing Authorisations for the medicinal products Lisinopril 2.5mg Tablets (PL 20092/0008), Lisinopril 5mg Tablets (PL 20092/0009), Lisinopril 10mg Tablets (PL 20092/0010), and Lisinopril 20mg Tablets (PL 20092/0011) on 20th June 2007. The products are prescription-only medicines.

These are abridged, standard, national applications for Lisinopril 2.5mg, 5mg, 10mg and 20mg Tablets. These are four strengths of lisinopril, submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the reference products, Zestril Tablets 2.5mg, 5mg, 10mg and 20mg respectively (PL 17901/0060, 0061, 0062 & 0063), granted to AstraZeneca UK Limited on 8th June 2000. These reference products were originally granted as PL 00029/0208, 0204, 0205 and 0206 respectively, authorised to Imperial Chemical Industries on 1st July 1993. The reference products have been authorised in the EEA for more than 10 years, so the period of data exclusivity has expired.

Lisinopril Tablets contain the active ingredient lisinopril, as lisinopril dihydrate, which belongs to a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors. The mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system. Lisinopril 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.

Lisinopril Tablets are used for the treatment of essential and renovascular hypertension; treatment of symptomatic heart failure; short-term treatment of haemodynamically stable patients following acute myocardial infarction; and treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy. The dose of losartan potassium to be used in these indications ranges from 2.5 to 80 mg daily.

These applications for Lisinopril 2.5mg, 5mg, 10mg and 20mg Tablets were submitted at the same time and they all depend on the single bioequivalence study presented comparing the applicant's 20mg product with the AstraZeneca reference product Zestril Tablets 20mg, sourced from France. Consequently, all sections of the Scientific Discussion refer to all four products. As the test products, Lisinopril 2.5mg, 5mg, 10mg and 20mg, were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20mg strength were extrapolated to the other tablet strengths.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

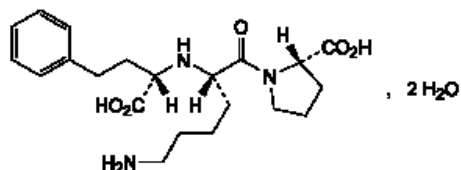
Lisinopril dihydrate

Nomenclature:

INN: Lisinopril dihydrate

Chemical name: (2S) - 1- [(2S)-6-amino -2- [[(1S) - 1 - carboxy - 3 - phenylpropyl] amino] hexanoyl] pyrrole - 2 - carboxylic acid

Structure:



Molecular formula: $C_{21}H_{31}N_3O_5 \cdot 2H_2O$

Molecular weight: 441.5

CAS No: 103577-45-3

Physical form: White to off white powder

Solubility: Lisinopril dihydrate is soluble in water, sparingly soluble in methanol, and practically insoluble in acetone and in ethanol

The active substance, lisinopril dihydrate, is the subject of a European Pharmacopoeia (EP) monograph.

All aspects of the manufacture and control of lisinopril dihydrate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of lisinopril dihydrate for inclusion in this medicinal product.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 48 months when stored in the proposed packaging.

DRUG PRODUCT

Description and Composition

The drug products are presented as round, biconvex, uncoated tablets with a scoreline on one side and a number representing the strength of the tablet on the other side. The tablets contain 2.5mg, 5mg, 10mg or 20mg of the active ingredient lisinopril, as lisinopril dihydrate.

Other ingredients consist of pharmaceutical excipients, namely mannitol, calcium hydrogen phosphate, maize starch, pregelatinised starch, colloidal anhydrous silica, and magnesium stearate. In addition, the 5mg, 10mg and 20mg strength tablets contain the excipient red iron oxide (E172). Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of red iron oxide (E172) which complies with a satisfactory in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been specified as being of vegetable origin. There are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Dissolution profiles

Dissolution profiles for the drug products were found to be similar to those for the reference products.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specification covering the 4 strengths is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The tablets are packed in PVC (polyvinyl chloride) / PVDC (polyvinylidene chloride) / aluminium foil blisters, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The products are packaged in pack sizes of 28 tablets.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. Storage conditions are “Store below 25°C” and “Store in the original package”.

Bioequivalence Study

A single bioequivalence study was submitted comparing the test product, Lisinopril 20mg Tablets, to the reference product, Zestril Tablets 20mg (AstraZeneca Reims).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory.

Conclusion

The test products are pharmaceutically equivalent to the reference products which have been licensed in the UK for over 10 years. The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Lisinopril 20mg Tablets is a generic medicinal product of Zestril Tablets 20mg appears justified. As the test products, Lisinopril 2.5mg, 5mg, 10mg and 20mg, meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20mg strength were extrapolated to the 2.5mg, 5mg and 10mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It is recommended that Marketing Authorisations are granted.

PRECLINICAL ASSESSMENT

These abridged applications, submitted under Article 10.1 of Directive 2001/83/EC, as amended, are for Lisinopril 2.5mg, 5mg, 10mg and 20mg Tablets, products claiming to be generic medicinal products of Zestril Tablets 2.5mg, 5mg, 10mg and 20mg (AstraZeneca UK Limited) respectively, which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

INDICATIONS

Lisinopril 2.5mg, 5mg, 10mg and 20mg Tablets are indicated for:

- Treatment of essential and renovascular hypertension.
- Treatment of symptomatic heart failure.
- Short-term treatment of haemodynamically stable patients following acute myocardial infarction.
- Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy.

The indications are consistent with those for the innovator product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the innovator product.

TOXICOLOGY

No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

Pharmacodynamics

No new pharmacodynamic data are presented and none are required.

Pharmacokinetics - Bioequivalence study

Only one bioequivalence study, using 20 mg tablets, has been submitted to cover all four tablet strengths. According to the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), this may be acceptable if the following conditions are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturer and process;
- The drug input has been shown to be linear over the therapeutic dose range;
- The qualitative composition of the different strengths is the same;
- The ratio between amounts of active substance and excipients is the same or, in the case of preparations containing a low concentration of active substance (less than 5%) the ratio between the amounts of excipients is similar
- The dissolution profile is similar under identical conditions for all strengths.

As the test products were deemed to meet the criteria specified in the Note for Guidance, the results and conclusions of the bioequivalence study on the 20mg strength were extrapolated to the 2.5mg, 5mg and 10mg tablet strengths.

The applicant presented a single bioequivalence study comparing the test product, Lisinopril 20mg Tablets, to the reference product, Zestril Tablets 20mg (AstraZeneca Reims). The design was a random, open label, two treatment, two period, two

sequence, single dose, crossover study conducted in healthy human adult male subjects under fasting conditions.

36 volunteers were recruited to the study. Only 32 subjects completed the study: one subject was withdrawn during the first period due to giddiness and hypotension, requiring intravenous fluids; two subjects failed to attend for the second period and one subject chose to withdraw before the second period. The Period 1 data for the last three of these subjects were included in analysis. Statistical analysis was performed on data from 31 subjects (one subject was excluded from statistical analysis).

A single oral dose of each drug was administered with an 8-day washout between dosing periods. Subjects were randomised to order of dosing. In each period, subjects were institutionalised from the evening before to 36 hours after dosing and were to return at 48 hours post-dosing for blood sampling. Subjects were fasted from 10 hours prior to dosing and appropriate restrictions on diet, fluid intake and concomitant medications were maintained.

Blood samples were taken at intervals appropriate to the known pharmacokinetic profile of the drug up to 48 hours after dosing and analysed for lisinopril concentration. The following pharmacokinetic parameters were reported: $AUC_{(0-\infty)}$, C_{max} , $AUC_{(0-t)}$, T_{max} , $T_{1/2}$ and K_{el} . Analysis of variance was conducted using subject, period, sequence and treatment as variables. 90% confidence intervals (CI) for the ratio of the least square means of the log-transformed values were presented and compared to the accepted range set down in CPMP/EWP/QWP/1401/98.

Biostudy Results:

| | | C_{max} (ng/mL) | AUC_{0-t} (ng.hr/mL) | $AUC_{0-\infty}$ (μ =ng.hr/mL) | $T_{max}(h)$ (mean) |
|----------|-----------------------|----------------------|---------------------------|--|------------------------|
| N | Test formulation | 31 | 30 | 30 | 31 |
| | Reference formulation | 31 | 31 | 31 | 31 |
| Mean | Test formulation | 105.333 | 1443.074 | 1488.612 | 6.58 |
| | Reference formulation | 106.989 | 1453.694 | 1494.676 | 6.10 |
| SD | Test formulation | 39.201 | 513.776 | 511.757 | 1.53 |
| | Reference formulation | 43.661 | 537.032 | 534.424 | 0.97 |
| C.V. (%) | Test formulation | 37.22 | 35.60 | 34.38 | 23.22 |
| | Reference formulation | 40.81 | 36.94 | 35.76 | 15.91 |

A summary of the results is represented below for log-transformed data:

Summary of comparative bioavailability - lisinopril

| Parameter (units) | LSM for test product | LSM for reference | Ratio (%) | 90% CI (parametric, %) |
|-------------------------------|----------------------|-------------------|-----------|------------------------|
| $\ln C_{\max}$ (ng/ml) | 97.92±39.20 | 96.90±43.66 | 101.32 | 90.24-113.76 |
| $\ln AUC_{(0-t)}$ (ng/h/ml) | 1336.77±513.78 | 1344.58±537.03 | 101.10 | 90.28-113.21 |
| $\ln AUC_{(0-inf)}$ (ng/h/ml) | 1388.34±511.75 | 1390.18±534.42 | 101.51 | 91.10-113.12 |

Overall conclusions on pharmacokinetics

The 90% confidence intervals for the ratio of the geometric means of the log-transformed values for $AUC_{(0-inf)}$, C_{\max} and $AUC_{(0-t)}$ was within the accepted 80-125% bioequivalence range for lisinopril. Bioequivalence was thus demonstrated for the 20mg tablet strength.

EFFICACY

Efficacy is reviewed in the Clinical Expert Report. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence.

No new efficacy data are required. The applicant has submitted a satisfactory literature review.

SAFETY

Safety is reviewed in the Clinical Expert Report.

No new safety data were submitted and none are required for these types of applications. The reference products are established and the main basis of the applications depends upon the bioequivalence study. The applicant has submitted a satisfactory literature review confirming the safety of lisinopril tablets. No new safety issues have been detected.

EXPERT REPORT

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics

The approved SmPCs are consistent with those for the innovator products and are acceptable.

Patient Information Leaflet

The PIL is in line with the approved SmPCs and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and bioequivalence of the 20mg strength test and reference products was shown with 90% Confidence Intervals within general acceptance limits. The conditions, as detailed in CPMP/EWP/QWP/1401/98, for a single bioequivalence study to cover multiple strengths of a product have been met, so the results and conclusions of this bioequivalence study were extrapolated to the 2.5mg, 5mg and 10mg strength tablets.

Sufficient clinical information has been submitted to support these applications. When used as indicated, lisinopril has a favourable benefit-to-risk ratio. Marketing Authorisations may be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Lisinopril 2.5mg, 5mg, 10mg and 20mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Lisinopril 20mg Tablets, and the reference product Zestril Tablets 20mg (AstraZeneca Reims). As the test products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 20mg strength were extrapolated to the 2.5mg, 5mg and 10mg tablet strengths. Thus, no separate bioequivalence studies were necessary for these strengths.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for Zestril Tablets 2.5mg, 5mg, 10mg and 20mg.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and the valid extrapolation of its results and conclusions support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with lisinopril dihydrate is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**LISINOPRIL 2.5MG, 5MG, 10MG & 20MG TABLETS
(LISINOPRIL DIHYDRATE)
PL 20092/0008, 0009, 0010 & 0011**

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation applications on 12th October 2005
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 3rd November 2005
- 3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 14th June 2006, and further information relating to the clinical dossiers on 26th July 2006
- 4 The applicant responded to the MHRA's requests, providing further information for the clinical sections on 1st February 2007 and further information for the quality sections on 2nd February 2007
- 5 Following assessment of the response the MHRA requested further information relating to the quality sections on 13th February 2007 and 24th April 2007
- 6 The applicant responded to the MHRA's request, providing further information for the quality sections on 12th April 2007 and 30th April 2007 respectively
- 7 The applications were determined on 20th June 2007

LISINOPRIL 2.5MG, 5MG, 10MG & 20MG TABLETS
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STEPS TAKEN AFTER AUTHORISATION

| Date submitted | Application type | Scope | Outcome |
|-----------------------|---|---|-----------------------------------|
| 20/12/2007 | Variation Pharmaceutical Type 1B National | To change the shelf life of the finished product from 2 years to 3 years. <i>This variation was submitted for all 4 PLs.</i> | Application granted 20/12/2007 |

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Lisinopril 2.5mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Lisinopril 2.5 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains Lisinopril Dihydrate equivalent to 2.5 mg of anhydrous Lisinopril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round tablets marked '2.5' on one side and scoreline on other side.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

Treatment of hypertension.

Heart failure

Treatment of symptomatic heart failure.

Acute myocardial infarction

Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.

Renal complications of diabetes mellitus

Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy (see section 5.1).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

The dose should be individualised according to patient profile and blood pressure response (see section 4.4).

Hypertension

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

Starting dose

In patients with hypertension the usual recommended starting dose is 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and /or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment (see Table 1 below).

Maintenance dose

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

Diuretic-treated patients

Symptomatic hypotension may occur following initiation of therapy with Lisinopril. This is more likely in patients who are being treated currently with diuretics. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Lisinopril. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Lisinopril should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Lisinopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5).

Dosage adjustment In renal impairment

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

Table 1 Dosage adjustment in renal impairment.

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

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

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

Heart failure

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

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

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Lisinopril. Renal function and serum potassium should be monitored (see section 4.4).

Acute myocardial infarction

Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with Lisinopril.

Starting dose (first 3 days after infarction)

Treatment with Lisinopril may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Lisinopril is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4).

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Maintenance dose

The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) Lisinopril should be withdrawn.

Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Lisinopril (see section 4.2)

Renal complications of diabetes mellitus

In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg Lisinopril once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg.

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Paediatric use

Efficacy and safety of use in children has not been fully established. Therefore, use in children is not recommended.

Use in the elderly

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

Use in kidney transplant patients

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to Lisinopril, to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema.
- Second or third trimesters of pregnancy (see section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Lisinopril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (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 those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia

or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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

Hypotension in acute myocardial infarction

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

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

As with other ACE inhibitors, Lisinopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1 in section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

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

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Lisinopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Lisinopril may be required.

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

Hypersensitivity/Angioedema

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

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis

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

Race

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

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

Cough

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

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see 4.5 Interaction with other medicinal products and other forms of interaction).

Lithium

The combination of lithium and Lisinopril is generally not recommended (see section 4.5).

Pregnancy and lactation

Lisinopril should not be used during the first trimester of pregnancy. Lisinopril is contraindicated in the second and third trimesters of pregnancy (see section 4.3). When pregnancy is detected, lisinopril treatment should discontinue as soon as possible (see section 4.6).

Use of lisinopril is not recommended during breast-feeding.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**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 supplements, potassium-sparing diuretics or potassium-containing salt substitutes

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia

include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

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

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of Lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid \geq 3g/day

Chronic administration of NSAIDs 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.

Other antihypertensive agents

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

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 effects of ACE inhibitors.

Antidiabetics

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

4.6 PREGNANCY AND LACTATION

Pregnancy

Lisinopril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester toxicity exposure have not appeared to manifest malformations consistent with human foetotoxicity as described below.

Lisinopril is contraindicated during the second and third trimester of pregnancy.

Prolonged ACE inhibitor 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 (see also section 5.3).

Should exposure to Lisinopril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken Lisinopril should be closely observed for hypotension, oliguria and hyperkalaemia. Lisinopril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

It is not known whether Lisinopril is excreted into human breast milk. Lisinopril is excreted into the milk of lactating rats. The use of Lisinopril is not recommended in women who are breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Lisinopril may have a minor or moderate effect on ability to drive and use machines. Patients who experience tiredness or dizziness should not drive or use machinery.

4.8 UNDESIRABLE EFFECTS

The following undesirable effects have been observed and reported during treatment with Lisinopril and other ACE inhibitors with the following frequencies: Very common ($\geq 10\%$), common ($\geq 1\%$, $< 10\%$), uncommon (≥ 0.1 , $< 1\%$), rare (≥ 0.01 , $< 0.1\%$), very rare ($< 0.01\%$) including isolated reports.

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.

very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease.

Metabolism and nutrition disorders:

very rare: hypoglycaemia.

Nervous system and psychiatric disorders:

common: dizziness, headache

uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.

rare: mental confusion.

Cardiac and vascular disorders:

common: orthostatic effects (including hypotension)

uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia. Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders:

common: cough

uncommon: rhinitis

very rare: bronchospasm, sinusitis. Allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:

common: diarrhoea, vomiting

- uncommon: nausea, abdominal pain and indigestion
- rare: dry mouth
- very rare: pancreatitis, intestinal angioedema, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4).

Skin and subcutaneous tissue disorders:

- uncommon: rash, pruritus
- rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis.
- very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

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.

Renal and urinary disorders:

- common: renal dysfunction
- rare: uraemia, acute renal failure
- very rare: oliguria/anuria.

Reproductive system and breast disorders:

- uncommon: impotence
- rare: gynaecomastia.

General disorders and administration site conditions:

- uncommon: fatigue, asthenia.

Investigations:

- uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia.
- rare: increases in serum bilirubin, hyponatraemia

4.9 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 4.4 special warning and precautions for use). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03.

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.

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.

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}).

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

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

Distribution

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

Elimination

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

Hepatic impairment

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

Renal impairment

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

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

Heart failure

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

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.

5.3 PRECLINICAL SAFETY DATA

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol

Calcium Hydrogen Phosphate

Maize Starch

Pregelatinised Starch

Colloidal Anhydrous Silica

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.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC / PVDC Aluminium blister packs in a carton in pack sizes of 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited

Suite 1, Victoria Court, Bexton Road

Knutsford

Cheshire WA16 0PF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20092/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/06/2007

10 DATE OF REVISION OF THE TEXT

20/12/2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Lisinopril 5mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Lisinopril 5 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains Lisinopril Dihydrate equivalent to 5 mg of anhydrous Lisinopril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pink, round tablets marked '5' on one side and scoreline on other side.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

Treatment of hypertension.

Heart failure

Treatment of symptomatic heart failure.

Acute myocardial infarction

Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.

Renal complications of diabetes mellitus

Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy (see section 5.1).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

The dose should be individualised according to patient profile and blood pressure response (see section 4.4).

Hypertension

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

Starting dose

In patients with hypertension the usual recommended starting dose is 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and /or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment (see Table 1 below).

Maintenance dose

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

Diuretic-treated patients

Symptomatic hypotension may occur following initiation of therapy with Lisinopril. This is more likely in patients who are being treated currently with diuretics. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Lisinopril. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Lisinopril should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Lisinopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5).

Dosage adjustment In renal impairment

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

Table 1 Dosage adjustment in renal impairment.

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

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

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

Heart failure

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

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

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Lisinopril. Renal function and serum potassium should be monitored (see section 4.4).

Acute myocardial infarction

Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with Lisinopril.

Starting dose (first 3 days after infarction)

Treatment with Lisinopril may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Lisinopril is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4).

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Maintenance dose

The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) Lisinopril should be withdrawn.

Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Lisinopril (see section 4.2)

Renal complications of diabetes mellitus

In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg Lisinopril once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg.

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Paediatric use

Efficacy and safety of use in children has not been fully established. Therefore, use in children is not recommended.

Use in the elderly

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

Use in kidney transplant patients

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to Lisinopril, to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema.
- Second or third trimesters of pregnancy (see section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Lisinopril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (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 those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia

or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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

Hypotension in acute myocardial infarction

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

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

As with other ACE inhibitors, Lisinopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1 in section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

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

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Lisinopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Lisinopril may be required.

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

Hypersensitivity/Angioedema

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

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis

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

Race

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

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

Cough

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

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see 4.5 Interaction with other medicinal products and other forms of interaction).

Lithium

The combination of lithium and Lisinopril is generally not recommended (see section 4.5).

Pregnancy and lactation

Lisinopril should not be used during the first trimester of pregnancy. Lisinopril is contraindicated in the second and third trimesters of pregnancy (see section 4.3). When pregnancy is detected, lisinopril treatment should discontinue as soon as possible (see section 4.6).

Use of lisinopril is not recommended during breast-feeding.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**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 supplements, potassium-sparing diuretics or potassium-containing salt substitutes

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia

include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

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

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of Lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid \geq 3g/day

Chronic administration of NSAIDs 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.

Other antihypertensive agents

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

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 effects of ACE inhibitors.

Antidiabetics

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

4.6 PREGNANCY AND LACTATION

Pregnancy

Lisinopril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester toxicity exposure have not appeared to manifest malformations consistent with human foetotoxicity as described below.

Lisinopril is contraindicated during the second and third trimester of pregnancy.

Prolonged ACE inhibitor 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 (see also section 5.3).

Should exposure to Lisinopril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken Lisinopril should be closely observed for hypotension, oliguria and hyperkalaemia. Lisinopril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

It is not known whether Lisinopril is excreted into human breast milk. Lisinopril is excreted into the milk of lactating rats. The use of Lisinopril is not recommended in women who are breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Lisinopril may have a minor or moderate effect on ability to drive and use machines. Patients who experience tiredness or dizziness should not drive or use machinery.

4.8 UNDESIRABLE EFFECTS

The following undesirable effects have been observed and reported during treatment with Lisinopril and other ACE inhibitors with the following frequencies: Very common ($\geq 10\%$), common ($\geq 1\%$, $< 10\%$), uncommon (≥ 0.1 , $< 1\%$), rare (≥ 0.01 , $< 0.1\%$), very rare ($< 0.01\%$) including isolated reports.

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.

very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease.

Metabolism and nutrition disorders:

very rare: hypoglycaemia.

Nervous system and psychiatric disorders:

common: dizziness, headache

uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.

rare: mental confusion.

Cardiac and vascular disorders:

common: orthostatic effects (including hypotension)

uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia. Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders:

common: cough

uncommon: rhinitis

very rare: bronchospasm, sinusitis. Allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:

common: diarrhoea, vomiting

uncommon: nausea, abdominal pain and indigestion

- rare: dry mouth
- very rare: pancreatitis, intestinal angioedema, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4).

Skin and subcutaneous tissue disorders:

- uncommon: rash, pruritus
- rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis.
- very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

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.

Renal and urinary disorders:

- common: renal dysfunction
- rare: uraemia, acute renal failure
- very rare: oliguria/anuria.

Reproductive system and breast disorders:

- uncommon: impotence
- rare: gynaecomastia.

General disorders and administration site conditions:

- uncommon: fatigue, asthenia.

Investigations:

- uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia.
- rare: increases in serum bilirubin, hyponatraemia.

4.9 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 4.4 special warning and precautions for use). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03.

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.

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.

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}).

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

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

Distribution

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

Elimination

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

Hepatic impairment

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

Renal impairment

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

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

Heart failure

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

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.

5.3 PRECLINICAL SAFETY DATA

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol

Calcium Hydrogen Phosphate

Red Iron Oxide (E172)

Maize Starch

Pregelatinised Starch

Colloidal Anhydrous Silica

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.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC / PVDC Aluminium blister packs in a carton in pack sizes of 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited

Suite 1, Victoria Court, Bexton Road

Knutsford

Cheshire WA16 0PF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20092/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/06/2007

10 DATE OF REVISION OF THE TEXT

20/12/2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Lisinopril 10mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Lisinopril 10 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains Lisinopril Dihydrate equivalent to 10 mg of anhydrous Lisinopril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pink, round tablets marked '10' on one side and scoreline on other side.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

Treatment of hypertension.

Heart failure

Treatment of symptomatic heart failure.

Acute myocardial infarction

Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.

Renal complications of diabetes mellitus

Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy (see section 5.1).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

The dose should be individualised according to patient profile and blood pressure response (see section 4.4).

Hypertension

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

Starting dose

In patients with hypertension the usual recommended starting dose is 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and /or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment (see Table 1 below).

Maintenance dose

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

Diuretic-treated patients

Symptomatic hypotension may occur following initiation of therapy with Lisinopril. This is more likely in patients who are being treated currently with diuretics. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Lisinopril. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Lisinopril should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Lisinopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5).

Dosage adjustment In renal impairment

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

Table 1 Dosage adjustment in renal impairment.

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

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

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

Heart failure

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

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

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Lisinopril. Renal function and serum potassium should be monitored (see section 4.4).

Acute myocardial infarction

Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with Lisinopril.

Starting dose (first 3 days after infarction)

Treatment with Lisinopril may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Lisinopril is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4).

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Maintenance dose

The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) Lisinopril should be withdrawn.

Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Lisinopril (see section 4.2)

Renal complications of diabetes mellitus

In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg Lisinopril once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg.

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Paediatric use

Efficacy and safety of use in children has not been fully established. Therefore, use in children is not recommended.

Use in the elderly

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

Use in kidney transplant patients

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to Lisinopril, to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema.
- Second or third trimesters of pregnancy (see section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Lisinopril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (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 those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia

or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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

Hypotension in acute myocardial infarction

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

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

As with other ACE inhibitors, Lisinopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1 in section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

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

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Lisinopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Lisinopril may be required.

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

Hypersensitivity/Angioedema

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

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis

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

Race

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

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

Cough

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

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see 4.5 Interaction with other medicinal products and other forms of interaction).

Lithium

The combination of lithium and Lisinopril is generally not recommended (see section 4.5).

Pregnancy and lactation

Lisinopril should not be used during the first trimester of pregnancy. Lisinopril is contraindicated in the second and third trimesters of pregnancy (see section 4.3). When pregnancy is detected, lisinopril treatment should discontinue as soon as possible (see section 4.6).

Use of lisinopril is not recommended during breast-feeding.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**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 supplements, potassium-sparing diuretics or potassium-containing salt substitutes

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia

include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

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

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of Lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid \geq 3g/day

Chronic administration of NSAIDs 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.

Other antihypertensive agents

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

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 effects of ACE inhibitors.

Antidiabetics

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

4.6 PREGNANCY AND LACTATION

Pregnancy

Lisinopril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester toxicity exposure have not appeared to manifest malformations consistent with human foetotoxicity as described below.

Lisinopril is contraindicated during the second and third trimester of pregnancy.

Prolonged ACE inhibitor 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 (see also section 5.3).

Should exposure to Lisinopril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken Lisinopril should be closely observed for hypotension, oliguria and hyperkalaemia. Lisinopril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

It is not known whether Lisinopril is excreted into human breast milk. Lisinopril is excreted into the milk of lactating rats. The use of Lisinopril is not recommended in women who are breast-feeding

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Lisinopril may have a minor or moderate effect on ability to drive and use machines. Patients who experience tiredness or dizziness should not drive or use machinery.

4.8 UNDESIRABLE EFFECTS

The following undesirable effects have been observed and reported during treatment with Lisinopril and other ACE inhibitors with the following frequencies: Very common ($\geq 10\%$), common ($\geq 1\%$, $< 10\%$), uncommon (≥ 0.1 , $< 1\%$), rare (≥ 0.01 , $< 0.1\%$), very rare ($< 0.01\%$) including isolated reports.

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.

very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease.

Metabolism and nutrition disorders:

very rare: hypoglycaemia.

Nervous system and psychiatric disorders:

common: dizziness, headache

uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.

rare: mental confusion.

Cardiac and vascular disorders:

common: orthostatic effects (including hypotension)

uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia. Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders:

common: cough

uncommon: rhinitis

very rare: bronchospasm, sinusitis. Allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:

common: diarrhoea, vomiting

- uncommon: nausea, abdominal pain and indigestion
- rare: dry mouth
- very rare: pancreatitis, intestinal angioedema, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4).

Skin and subcutaneous tissue disorders:

- uncommon: rash, pruritus
- rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis.
- very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

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.

Renal and urinary disorders:

- common: renal dysfunction
- rare: uraemia, acute renal failure
- very rare: oliguria/anuria.

Reproductive system and breast disorders:

- uncommon: impotence
- rare: gynaecomastia.

General disorders and administration site conditions:

- uncommon: fatigue, asthenia.

Investigations:

- uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia.
- rare: increases in serum bilirubin, hyponatraemia.

4.9 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 4.4 special warning and precautions for use). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03.

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.

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.

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}).

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

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

Distribution

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

Elimination

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

Hepatic impairment

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

Renal impairment

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

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

Heart failure

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

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.

5.3 PRECLINICAL SAFETY DATA

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol

Calcium Hydrogen Phosphate

Red Iron Oxide (E172)

Maize Starch

Pregelatinised Starch

Colloidal Anhydrous Silica

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.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC / PVDC Aluminium blister packs in a carton in pack sizes of 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited

Suite 1, Victoria Court, Bexton Road

Knutsford

Cheshire WA16 0PF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20092/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/06/2007

10 DATE OF REVISION OF THE TEXT

20/12/2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Lisinopril 20mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Lisinopril 20 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains Lisinopril Dihydrate equivalent to 20 mg of anhydrous Lisinopril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pink, round tablets marked '20' on one side and scoreline on other side.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

Treatment of hypertension.

Heart failure

Treatment of symptomatic heart failure.

Acute myocardial infarction

Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.

Renal complications of diabetes mellitus

Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy (see section 5.1).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

The dose should be individualised according to patient profile and blood pressure response (see section 4.4).

Hypertension

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

Starting dose

In patients with hypertension the usual recommended starting dose is 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and /or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment (see Table 1 below).

Maintenance dose

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

Diuretic-treated patients

Symptomatic hypotension may occur following initiation of therapy with Lisinopril. This is more likely in patients who are being treated currently with diuretics. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Lisinopril. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Lisinopril should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Lisinopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5).

Dosage adjustment In renal impairment

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

Table 1 Dosage adjustment in renal impairment.

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

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

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

Heart failure

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

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

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Lisinopril. Renal function and serum potassium should be monitored (see section 4.4).

Acute myocardial infarction

Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with Lisinopril.

Starting dose (first 3 days after infarction)

Treatment with Lisinopril may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Lisinopril is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4).

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Maintenance dose

The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) Lisinopril should be withdrawn.

Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Lisinopril (see section 4.2)

Renal complications of diabetes mellitus

In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg Lisinopril once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg.

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Paediatric use

Efficacy and safety of use in children has not been fully established. Therefore, use in children is not recommended.

Use in the elderly

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

Use in kidney transplant patients

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to Lisinopril, to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema.
- Second or third trimesters of pregnancy (see section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Lisinopril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (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 those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia

or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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

Hypotension in acute myocardial infarction

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

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

As with other ACE inhibitors, Lisinopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1 in section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

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

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Lisinopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Lisinopril may be required.

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

Hypersensitivity/Angioedema

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

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis

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

Race

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

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

Cough

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

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see 4.5 Interaction with other medicinal products and other forms of interaction).

Lithium

The combination of lithium and Lisinopril is generally not recommended (see section 4.5).

Pregnancy and lactation

Lisinopril should not be used during the first trimester of pregnancy. Lisinopril is contraindicated in the second and third trimesters of pregnancy (see section 4.3). When pregnancy is detected, lisinopril treatment should discontinue as soon as possible (see section 4.6).

Use of lisinopril is not recommended during breast-feeding.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**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 supplements, potassium-sparing diuretics or potassium-containing salt substitutes

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia

include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

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

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of Lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid \geq 3g/day

Chronic administration of NSAIDs 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.

Other antihypertensive agents

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

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 effects of ACE inhibitors.

Antidiabetics

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

4.6 PREGNANCY AND LACTATION

Pregnancy

Lisinopril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester toxicity exposure have not appeared to manifest malformations consistent with human foetotoxicity as described below.

Lisinopril is contraindicated during the second and third trimester of pregnancy.

Prolonged ACE inhibitor 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 (see also section 5.3).

Should exposure to Lisinopril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken Lisinopril should be closely observed for hypotension, oliguria and hyperkalaemia. Lisinopril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

It is not known whether Lisinopril is excreted into human breast milk. Lisinopril is excreted into the milk of lactating rats. The use of Lisinopril is not recommended in women who are breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Lisinopril may have a minor or moderate effect on ability to drive and use machines. Patients who experience tiredness or dizziness should not drive or use machinery.

4.8 UNDESIRABLE EFFECTS

The following undesirable effects have been observed and reported during treatment with Lisinopril and other ACE inhibitors with the following frequencies: Very common ($\geq 10\%$), common ($\geq 1\%$, $< 10\%$), uncommon (≥ 0.1 , $< 1\%$), rare (≥ 0.01 , $< 0.1\%$), very rare ($< 0.01\%$) including isolated reports.

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.

very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease.

Metabolism and nutrition disorders:

very rare: hypoglycaemia.

Nervous system and psychiatric disorders:

common: dizziness, headache

uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.

rare: mental confusion.

Cardiac and vascular disorders:

common: orthostatic effects (including hypotension)

uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia. Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders:

common: cough

uncommon: rhinitis

very rare: bronchospasm, sinusitis. Allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:

common: diarrhoea, vomiting

- uncommon: nausea, abdominal pain and indigestion
- rare: dry mouth
- very rare: pancreatitis, intestinal angioedema, hepatitis - either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4).

Skin and subcutaneous tissue disorders:

- uncommon: rash, pruritus
- rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis.
- very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

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.

Renal and urinary disorders:

- common: renal dysfunction
- rare: uraemia, acute renal failure
- very rare: oliguria/anuria.

Reproductive system and breast disorders:

- uncommon: impotence
- rare: gynaecomastia.

General disorders and administration site conditions:

- uncommon: fatigue, asthenia.

Investigations:

- uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia.
- rare: increases in serum bilirubin, hyponatraemia.

4.9 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 4.4 special warning and precautions for use). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03.

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.

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.

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}).

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

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

Distribution

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

Elimination

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

Hepatic impairment

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

Renal impairment

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

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

Heart failure

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

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.

5.3 PRECLINICAL SAFETY DATA

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol

Calcium Hydrogen Phosphate

Red Iron Oxide (E172)

Maize Starch

Pregelatinised Starch

Colloidal Anhydrous Silica

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.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC / PVDC Aluminium blister packs in a carton in pack sizes of 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited

Suite 1, Victoria Court, Bexton Road

Knutsford

Cheshire WA16 0PF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20092/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/06/2007

10 DATE OF REVISION OF THE TEXT

20/12/2007

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET LISINOPRIL 2.5 MG, 5 MG, 10 MG AND 20 MG TABLETS

Lisinopril Dihydrate

Please read all of this leaflet carefully before you start taking this medicine. It is an important source of information about your medicine and how to take it safely.

- 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 personally and you should 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 on this leaflet, please tell your doctor or pharmacist.

In This Leaflet:

- 1 What Lisinopril Tablets are and what they are used for.
- 2 Before you take Lisinopril Tablets.
- 3 How to take this medicine.
- 4 Possible side effects.
- 5 How to store this medicine.
- 6 Further information.

1. WHAT LISINOPRIL TABLETS ARE AND WHAT THEY ARE USED FOR

Lisinopril belongs to a group of medicines called ACE inhibitors (Angiotensin Converting Enzyme inhibitors). Lisinopril works by widening your blood vessels, which helps reduce your blood pressure and makes it easier for your heart to pump blood to all parts of your body. Your doctor has prescribed Lisinopril for one of the following reasons:

- Your blood pressure is too high (hypertension).
- You have a heart condition known as symptomatic heart failure, where the heart does not pump your blood around your body as well as it should.
- You have had a heart attack (myocardial infarction) that may lead to a weakening of your

heart. Lisinopril slows the weakening down.

- You have kidney problems related to your diabetes and high blood pressure.

2. BEFORE YOU TAKE LISINOPRIL TABLETS

Do not take Lisinopril

- If you are pregnant.
- If you have previously been treated with a medicine in the same group of drugs as Lisinopril (ACE inhibitors) and have had an allergic reaction which caused swelling of the hands, feet, or ankles, the face, lips, tongue and/or throat with difficulty in swallowing or breathing or if you or a member of your family have had a similar reaction.
- If you have ever had an allergic reaction to Lisinopril or to any of its other ingredients.

If you are not sure whether to start taking Lisinopril, talk to your doctor.

Take special care with Lisinopril

Tell your doctor if you have or have had any medical condition, especially the following:

- A narrowing of the aorta (aortic stenosis), the kidney artery (renal artery stenosis) or the heart valves (mitral valve stenosis), or an increase in the thickness of the heart muscle (hypertrophic cardiomyopathy, HOCM).
- Other health problems such as:
 - Low blood pressure (you may notice this as dizziness or lightheadedness especially when standing).
 - Kidney disease or you are undergoing dialysis.
 - Liver disease.
 - Blood vessel disease (collagen vascular disease) and/or treatment with allopurinol (for gout), procainamide (for abnormal heartbeats), immunosuppressants (medicines which suppress the body's immune response), diuretics and drugs which increase potassium levels (including heparin).
 - Diarrhoea or vomiting.
 - A salt-restricted diet or you are taking potassium supplements.

Stop taking Lisinopril and seek medical attention immediately if any of the following situations occur (an allergic reaction):

- If you develop difficulty in breathing with or without swelling of the face, lips, tongue and/or throat.

- If you develop swelling of the face, lips, tongue and/or throat which may cause difficulty in swallowing.
- If you develop severe itching of the skin (with raised lumps).

Tell your doctor if you are undergoing/or will undergo desensitisation treatment for an allergy, for example, to insect stings. The desensitisation treatment reduces the effects of the allergy (e.g. bee or wasp stings) but sometimes it can cause a more severe allergic reaction if you are taking ACE inhibitors during the desensitisation treatment.

Tell your doctor if you are going into hospital for an operation. Tell your doctor or dentist that you are taking Lisinopril before you are given a local or general anaesthetic. Lisinopril, combined with some anaesthetics, may cause a short-term drop in blood pressure so on after taking the tablets.

Take special care when taking the first dose of Lisinopril. It may cause a greater fall in blood pressure than will occur following continued treatment. You may notice this as dizziness or lightheadedness and it may help to lie down. If you are concerned, please consult your doctor.

Do not give Lisinopril to children under 18 years. There is limited information on the safety and effectiveness of Lisinopril in children.

Taking Lisinopril with other medicines

Tell your doctor if you are taking or have recently taken any other medicines, including herbal remedies, health foods or supplements that you have bought yourself. This also applies to medicines used some time ago. Some medicines may affect the actions of other medicines. Talk to your doctor if you are taking any of the following medicines:

- Diuretics (water tablets including those which conserve potassium).
- Other medicines for your high blood pressure (antihypertensives).
- Non-steroidal anti-inflammatory medicines (NSAIDs) such as indometacin and high doses of aspirin (more than 3 grams per day), which are used to treat arthritis or muscle pain.
- Medicines for mental disorders such as lithium, antipsychotics or tricyclic antidepressants.
- Potassium tablets or potassium containing salt substitutes.
- Medicines for the treatment of diabetes, such as insulin or those taken orally, to lower blood sugar.
- Medicines that stimulate the central nervous

system (sympathomimetics). These include ephedrine, pseudoephedrine and salbutamol and maybe found in some decongestants, cough/cold remedies and asthma medication.

- Medicines that suppress the body's immune response (immunosuppressants), treatment with allupurinol (for gout) or procainamide (for abnormal heartbeats).

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or intend to become pregnant. Lisinopril must not be taken during pregnancy.

Tell your doctor if you are breast feeding or intend to breast-feed. Lisinopril should not be used whilst breastfeeding.

Driving and using machines

Lisinopril may have a minor or moderate effect on ability to drive and use machines. Patients who experience tiredness or dizziness should not drive or use machinery.

If you are not sure whether you should start taking Lisinopril, contact your doctor.

3. HOW TO TAKE LISINOPRIL TABLETS

How much to take

Your doctor will tell you how many tablets to take each day. The dosage is individual and it is important that you take it as prescribed by your doctor. Your starting dose and long term dose will depend on your medical condition and whether you are taking any other medicines. Check with your doctor or pharmacist if you are unsure.

For raised blood pressure

The usual recommended starting dose is 10 mg taken once a day. The usual long-term dose is 20 mg taken once a day.

For symptomatic heart failure

The usual recommended starting dose is 2.5 mg taken once a day. The usual long term dose is 5 to 35 mg taken once a day.

After a heart attack

The usual recommended starting dose is 5 mg on day 1 and day 2, then 10 mg taken once a day.

For problems related to diabetes

The usual dose is either 10 mg or 20 mg taken once a day.

How to take Lisinopril

- Swallow the tablet with a drink of water.
- Try to take your tablets at the same time each day. It does not matter if you take Lisinopril before or after food.
- Do not stop taking your tablets if you are feeling well, unless your doctor tells you.
- Remember, the first dose of Lisinopril may cause a greater fall in blood pressure than will occur following continued treatment. This is especially likely if patients are also taking diuretics. You may notice this as dizziness or lightheadedness and it may help to lie down. If concerned, please consult your doctor as soon as possible.
- If you have the impression that the effect of Lisinopril is too strong or too weak, talk to your doctor or pharmacist as soon as possible.

If you take more Lisinopril than you should

Contact your doctor or nearest hospital immediately if you have taken more than you should (overdose).

If you forget to take a dose

If you miss a dose, do not take an extra dose to make up for the missed dose. Just resume your usual schedule.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Lisinopril can cause side effects. Do not be alarmed by this list of possible side effects, you may not have any of them. Most patients do not notice any side effects. However if you do and they bother you, talk to your doctor.

Common side effects that may occur (between 1 in 10 and 1 in 100 patients):

Headache
Dizziness or light-headedness especially when standing up quickly
Diarrhoea
Cough
Vomiting

Lisinopril may affect the kidneys, causing abnormally low or no urine to be passed.

Uncommon side effects that may occur (between 1 in 100 and 1 in 1,000 patients):

Mood changes
Change of colour (pale blue followed by redness) and/or numbness or tingling in the fingers or toes
Changes in the way things taste
Feeling sleepy or difficulty in going to sleep, strange dreams
Rapid heart beat
Running nose
Nausea
Stomach pain or indigestion
Skin rash
Itching
Impotence
Tiredness
Weakness (loss of strength).

An excessive drop in blood pressure may be experienced in patients with coronary heart disease, or those with a narrowing of the aorta (aortic stenosis), the kidney artery (renal artery stenosis) or the heart valves (mitral valve stenosis), or those patients with an increase in the thickness of the heart muscle (hypertrophic cardiomyopathy).

Rare side effects that may occur (between 1 in 1,000 and 1 in 10,000 patients):

Allergic reactions: Stop taking Lisinopril and seek medical attention immediately if any of the following situations occur:

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

Rarely, there may be changes to some of the cells or other parts of your blood. It is possible that your doctor may occasionally take blood samples to check whether Lisinopril has had any effect on your blood. Sometimes these changes may show themselves as tiredness or a sore throat, or they may be accompanied by a fever, joint and muscle pains, swelling of the joints or glands, or sensitivity to sunlight.

Other rare side effects are:

Confusion
Dry mouth

Hair loss
 Psoriasis
 Development of breasts in men.

Very rare side effects that may occur (less than 1 in 10,000 patients)

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.

Tell your doctor if you have any side effects that are not mentioned in this leaflet.

5. HOW TO STORE LISINOPRIL TABLETS

Store below 25°C. Store in the original package.

Do not take your tablets after the expiry date stated on the label. The expiry date refers to the last day of that month.

Return any unused Lisinopril tablets to your pharmacist.

Keep out of the reach and sight of children.

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 Lisinopril Tablet contains

The active substance is Lisinopril Dihydrate.
 The other ingredients are Mannitol, Calcium Hydrogen Phosphate, Maize Starch, Pregelatinised Starch, Colloidal Anhydrous Silica, Magnesium Stearate and in the case of 5mg, 10 mg and 20 mg tablets, Red Iron Oxide (E172).

What Lisinopril Tablets looks like and contents of the pack

Lisinopril tablets are supplied in 4 strengths:

2.5 mg, 5 mg, 10 mg, 20 mg

The 2.5 mg tablets are white, round tablets and the 5mg, 10 mg and 20 mg tablets are pink, round tablets. The tablets have a number denoting tablet strength on one side and a scoreline on the other.

They are supplied as PVC / PVDC Aluminium blister packs in a carton in pack sizes of 28 tablets.

Marketing Authorization Holder and Manufacturer

The Marketing Authorisation Holder:

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 Tel.: + 44 (0) 1565 751378.

Manufacturer:

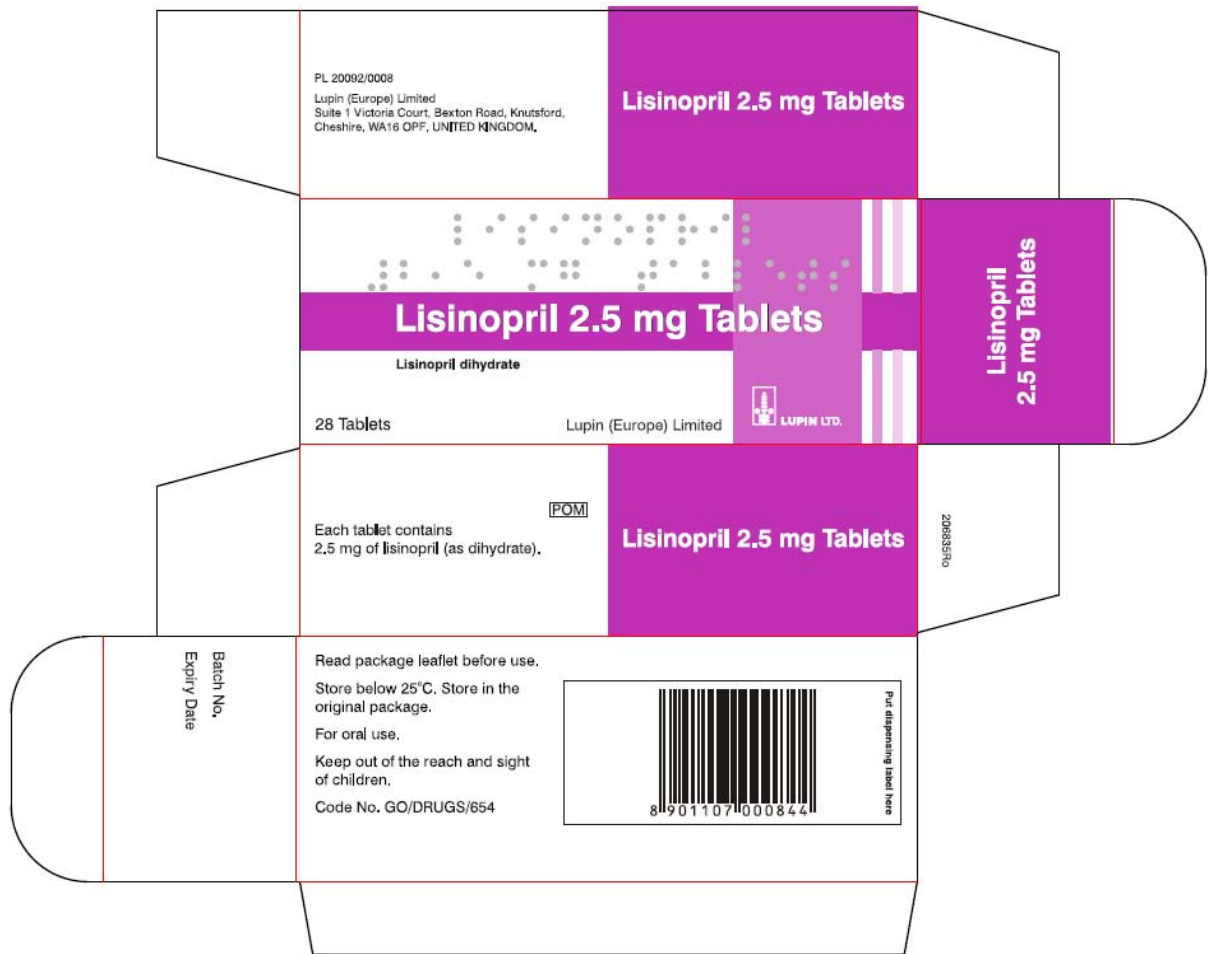
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Date of preparation: January 2007

LABELLING
Lisinopril 2.5mg Tablets
 Carton for blisters, with braille



Blister foil



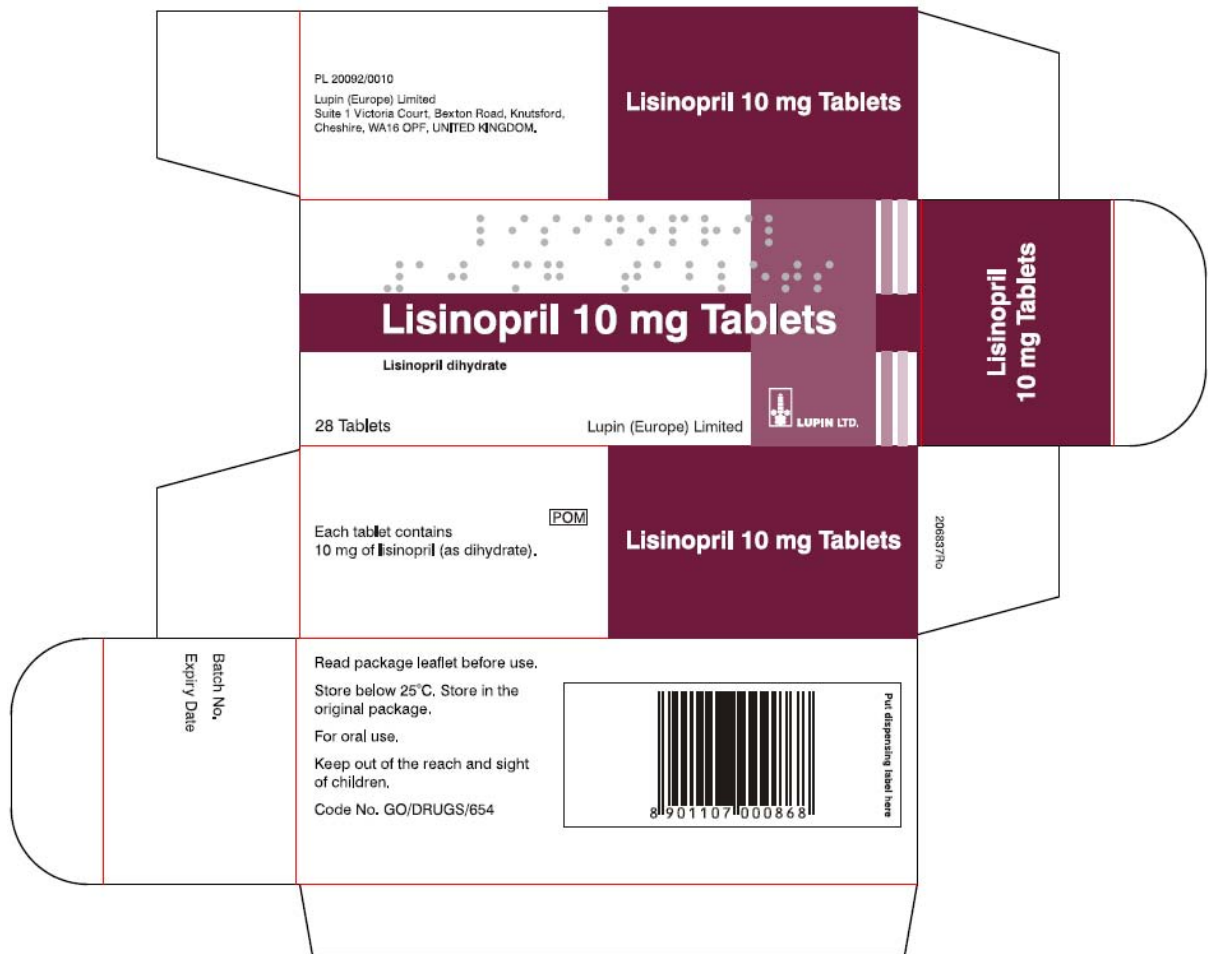
Lisinopril 5mg Tablets
Carton for blisters, with braille



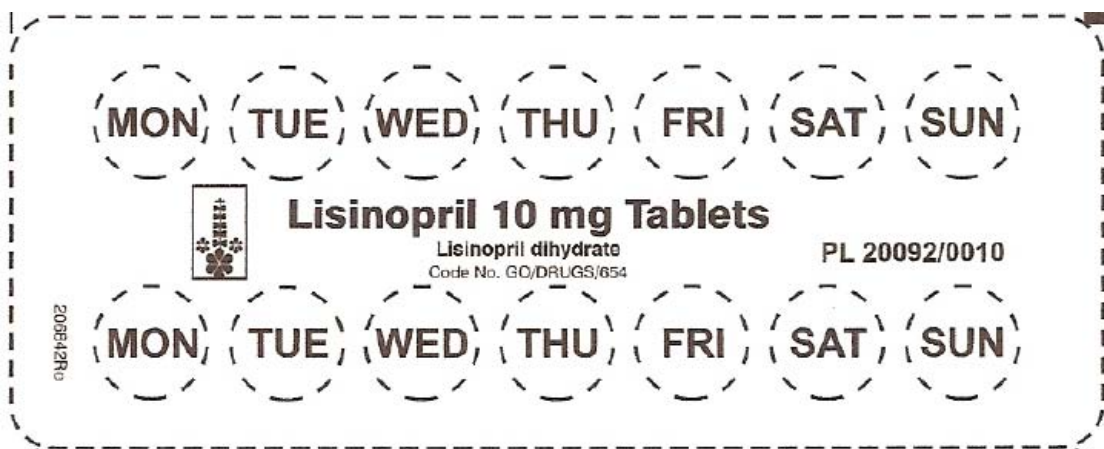
Blister foil



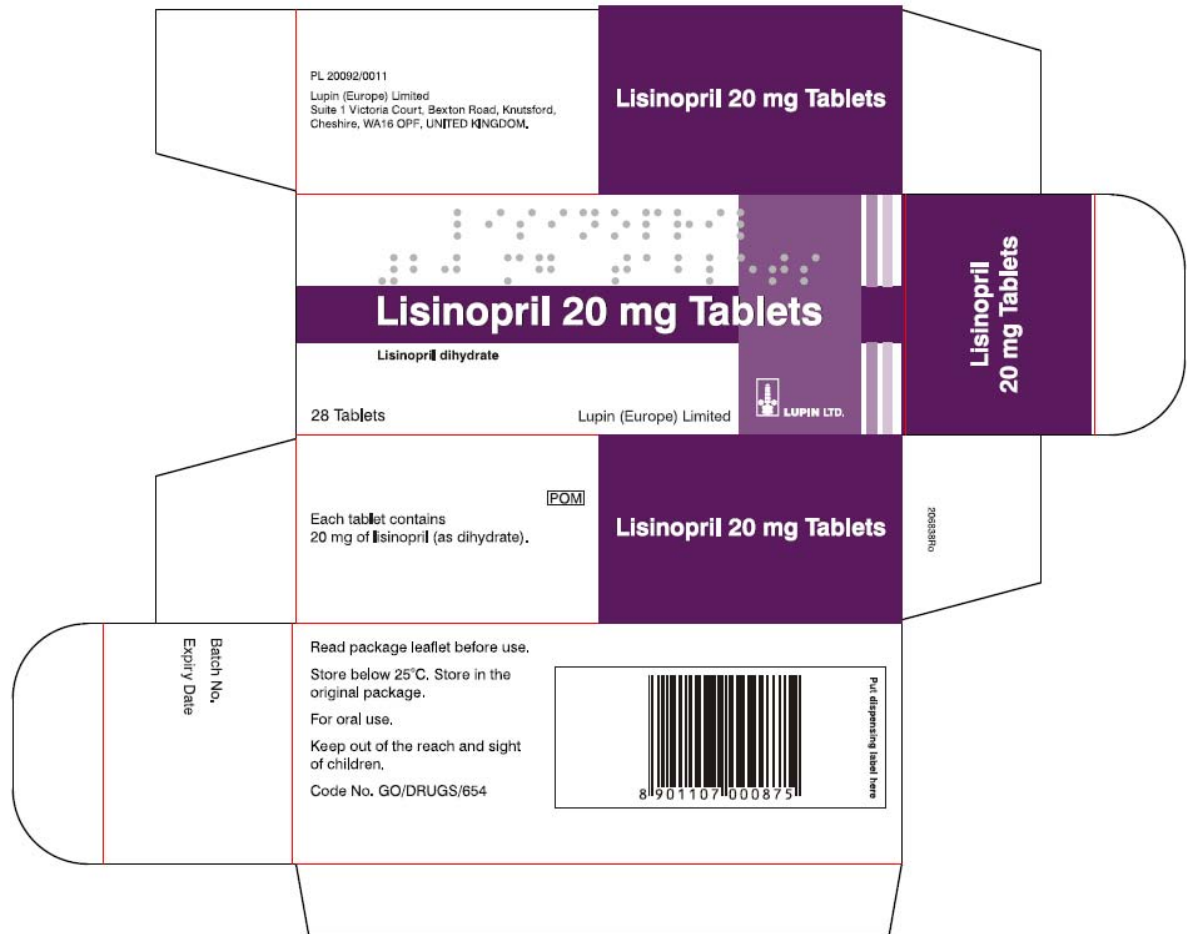
Lisinopril 10mg Tablets
Carton for blisters, with braille



Blister foil



Lisinopril 20mg Tablets
Carton for blisters, with braille



Blister foil

