Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets

PL 20092/0027-8
UKPAR

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On 3rd November 2009, the MHRA granted Lupin (UK) Limited Marketing Authorisations (licences) for Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets and Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets (PL 20092/0027-8).

This medicine is used to treat high blood pressure. This medicine contains lisinopril and hydrochlorothiazide. Lisinopril belongs to a group of medicines called ‘ACE inhibitors’. These work by widening blood vessels which makes it easier for the heart to pump blood through them, to all parts of the body.

Hydrochlorothiazide belongs to a group of medicines called water tablets. These work by increasing the amount of urine made by the kidneys.

Lisinopril and hydrochlorothiazide reduce blood pressure in a different way.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets and Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
**Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets**

**Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets**

**PL 20092/0027-8**

**SCIENTIFIC DISCUSSION**

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INTRODUCTION

The UK granted Lupin (UK) Limited Marketing Authorisations for the medicinal products Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets and Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets (PL 20092/0027-8) on 3rd November 2009. The products are prescription only medicines (POM) indicated for the management of mild to moderate hypertension in patients who have been stabilised on the individual components given in the same proportions.

These applications for Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets and Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Zestoretic 10 and Zestoretic 20 Tablets, first authorised in the UK to Zeneca Limited (PL 12619/0091 and 83) in January 1994. These underwent a change of ownership on 8th June 2000 to AstraZeneca UK Limited (PL 17901/0058-9).

The product contains lisinopril, which is an angiotensin-converting enzyme (ACE) inhibitor and hydrochlorothiazide, which is a thiazide diuretic.

Hypertension is a major determinant of cardiovascular mortality and morbidity. It is a significant risk factor for coronary atherosclerosis, a major determinant of incidence of strokes/cerebrovascular accidents at all ages and especially in the elderly. Therefore control of hypertension is an important aspect of improving cardiovascular mortality and morbidity. In recent years, combination products or combination therapy have made significant advances in achieving such control. In several instances, combination treatment using two different classes achieves better control of blood pressure in both short and long term. The combination of lisinopril and hydrochlorothiazide is one such well established combination.
UKPAR Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets
PL 20092/0027-8

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Lisinopril
INN: Lisinopril dihydrate
Chemical name: (i) (2S)-1-[(2S)-6-amino-2-[[1(S)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrole-2-carboxylic acid
(ii) N-[N-[(1S)-1-carboxy-3-phenylpropyl]-L-lysyl]-L-proline

Structure:

Physical form: A white or almost white crystalline powder.
Solubility: Soluble in water, sparingly soluble in methanol, practically insoluble in acetone and in ethanol.

Molecular formula: C_{21}H_{31}N_{3}O_{5}.2H_{2}O
Molecular weight: 441.5

Hydrochlorothiazide
INN: Hydrochlorothiazide
Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide

Structure:

Physical form: A white or almost white crystalline powder.
Solubility Soluble in acetone and dilute solutions of alkali hydroxides

Molecular formula: C_{7}H_{8}ClN_{3}O_{4}S_{2}
Molecular weight: 297.7

Appropriate specifications based on the European Pharmacopoeia has been provided for lisinopril and hydrochlorothiazide.
All aspects of the manufacture of the active substances lisinopril and hydrochlorothiazide from their starting materials are controlled by Certificates of Suitability.

Appropriate retest periods have been proposed based on stability data submitted for the active substances lisinopril and hydrochlorothiazide.

Appropriate specifications are provided for the active substances, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredients. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substances to be physically and chemically stable drugs, and supporting appropriate retest periods.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients mannitol (E 421), calcium hydrogen phosphate dihydrate, maize starch, pregelatinised starch, magnesium stearate, yellow iron oxide and FD & C Blue No. 2 Aluminium Lake.

All the ingredients with the exception of yellow iron oxide and FD & C Blue No. 2 Aluminium Lake comply with their relevant European Pharmacopoeia monographs. Yellow iron oxide and FD & C Blue No. 2 Aluminium Lake comply with in-house specifications.

None of the excipients used contain material of animal or human origin. The magnesium stearate contained in this product is sourced from vegetable origin and therefore no European Pharmacopoeia Certificates of suitability for TSE is required.

**Product development**

The objective of the development programme was to produce products that could be considered generic medicinal products of Zestoretic 10 and Zestoretic 20 Tablets (AstraZeneca (UK) Limited).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative dissolution and impurity profiles have been provided for the finished product versus the reference products.

**Manufacture**

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on three pilot scale batches of finished product and the results appear satisfactory. The applicant has committed to perform process validation on three future commercial-scale batches.
Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis for all working standards used have been provided and are satisfactory.

Container-Closure System
The product is packaged in polyvinylchloride, polyvinylidene chloride and aluminium foil blister packs in cartons.
The product comes in pack sizes of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 and 500 tablets.

Specifications and certificates of analysis have been provided. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 2 years has been set, with storage conditions ‘Store below 30°C’ and ‘Store in the original carton in order to protect from light’, which is satisfactory.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
These are pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

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, as amended. 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.

MAA Form
These are pharmaceutically satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications for Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets and Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets are submitted as abridged standard applications according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal products of Zestoretic 10 and Zestoretic 20 Tablets, first authorised in the UK to Zeneca Limited (PL 12619/0091 and 83) in January 1994. These underwent a change of ownership on 8th June 2000 to AstraZeneca UK Limited (PL 17901/0058-9).

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

CLINICAL PHARMACOLOGY
To support the applications, the marketing authorisation holder has included a single bioequivalence study:

An open-label, randomized, 2-period, 2 sequence, crossover bioequivalence study comparing the pharmacokinetics of Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets (Test) versus Zestoretic 20mg/12.5mg Tablets (Reference) under fasted conditions.

Blood sampling was performed pre-drug administration, during the study and up to 72 hours post dose in each treatment period. There was a washout period of 10 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values: Geometric Least Mean Squares and 90% Confidence Interval

Pharmacokinetic parameters of Lisinopril

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀-t (ng/ml/h)</th>
<th>AUC₀-∞ (ng/ml/h)</th>
<th>C_max (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>1262.112 ± 583.146</td>
<td>1320.465 ± 580.096</td>
<td>88.345 ± 43.928</td>
</tr>
<tr>
<td>Reference</td>
<td>1331.195 ± 499.762</td>
<td>1386.204 ± 501.782</td>
<td>93.353 ± 38.075</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>94.81 (88.26-101.84)</td>
<td>95.26 (88.98-101.98)</td>
<td>94.64 (87.60-102.24)</td>
</tr>
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Pharmacokinetic parameters of Hydrochlorothiazide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀-t (ng/ml/h)</th>
<th>AUC₀-∞ (ng/ml/h)</th>
<th>C_max (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>751.659 ± 157.215</td>
<td>786.555 ± 162.927</td>
<td>96.267 ± 24.823</td>
</tr>
<tr>
<td>Reference</td>
<td>754.385 ± 171.711</td>
<td>789.504 ± 176.107</td>
<td>98.273 ± 22.960</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>99.64 (96.31-103.08)</td>
<td>99.63 (96.40-102.96)</td>
<td>97.96 (92.87-103.33)</td>
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The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC₀-t and C_max for hydrochlorothiazide and lisinopril lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.
**EFFICACY**
No new data has been provided.

**SAFETY**
No new data has been provided.

**EXPERT REPORTS**
The clinical expert report has been written by a suitably qualified person and is satisfactory.

**PATIENT INFORMATION LEAFLET (PIL)**
This is consistent with that for the reference product and is satisfactory.

**LABELLING**
These are satisfactory.

**APPLICATION FORMS (MAA)**
These are satisfactory.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
These are consistent with those for the reference products and are satisfactory.

**DISCUSSION**
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

**MEDICAL CONCLUSION**
The bioequivalence study submitted has shown that Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets and Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets can be considered as generic medicinal products to the originator products Zestoretic 10 and Zestoretic 20 Tablets (AstraZeneca (UK) Limited).

The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets and Lisinopril and Hydrochlorothiazide 20mg/12.5mg 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 and Hydrochlorothiazide 20mg/12.5mg Tablets and the reference product. As these products 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 Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets can be extrapolated to Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with lisinopril and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
STEPS TAKEN FOR ASSESMENT

1. The MHRA received the marketing authorisation applications on 4th April 2006.

2. Following standard checks and communication with the applicant, the MHRA considered the applications valid on 11th May 2006.

3. Following assessment of the applications, the MHRA requested further information on the clinical sections of the dossier on 8th December 2006. Further information was requested by the MHRA on the quality sections of the dossier on 28th July 2006, 27th February 2007 and 30th August 2007.

4. The applicant responded to the MHRA’s requests, providing further information on the clinical sections of the dossier on 8th August 2007. Further information was provided by the applicant on the quality sections of the dossier on 27th February 2007, 15th August 2007 and 8th October 2007.

5. The applications were determined on 3rd November 2009.
Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets

Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets

PL 20092/0027-8

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

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<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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UKPAR Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets
PL 20092/0027-8

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Tablet contains:
Lisinopril dihydrate equivalent to anhydrous Lisinopril 10mg and Hydrochlorothiazide 12.5mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
Blue, hexagonal tablets, plain on both sides

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets is indicated in the management of mild to moderate hypertension in patients who have been stabilised on the individual components given in the same proportions.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route of administration: Oral

Essential Hypertension
The usual dosage is one tablet, administered once daily. As with all other medication taken once daily, Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets should be taken at approximately the same time each day.
In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks at this dose level, the dose can be increased to two tablets administered once daily.

Use in the elderly
In clinical studies the efficacy and tolerability of lisinopril and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients. Lisinopril was equally effective in elderly (65 years or older) and non-elderly hypertensive patients. In elderly hypertensive patients, monotherapy with lisinopril was as effective in reducing diastolic blood pressure as monotherapy with either hydrochlorothiazide or atenolol. In clinical studies, age did not affect the tolerability of lisinopril.

Use in children
Safety and effectiveness in children have not been established.

Dosage in Renal Insufficiency
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30ml/min or below (i.e. moderate or severe renal insufficiency).

Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets is not to be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of >30 and <80ml/min, Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets may be used, but only after titration of the individual components.

Prior Diuretic Therapy
Symptomatic hypotension may occur following the initial dose of Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets; this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets. If this is not possible, treatment should be started with lisinopril alone, in a 2.5 mg dose.
4.3 CONTRAINDICATIONS

Lisinopril
Hypersensitivity to lisinopril, or any other angiotensin converting enzyme (ACE) inhibitor
History of angioedema associated with previous ACE inhibitor therapy
Hereditary or idiopathic angioedema
Second and third trimesters of pregnancy (see sections 4.4 and 4.6)

Hydrochlorothiazide
History of hypersensitivity to hydrochlorothiazide or other sulphonamide-derived drugs
Severe renal impairment (creatinine clearance <30ml/min)
Severe hepatic impairment
Second or third trimesters of pregnancy (see section 4.6)
Lactation (see section 4.6)

Lisinopril/Hydrochlorothiazide combination
Hypersensitivity to lisinopril, hydrochlorothiazide or to any of the excipients
Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets is contraindicated in patients with anuria or aortic stenosis or hyperkalaemia.

The use of Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets during pregnancy is not recommended. When pregnancy is detected Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets should be discontinued as soon as possible, unless it is considered life-saving for the mother.

Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets is contraindicated in lactating women who are breast-feeding infants. It is not known whether lisinopril is excreted in human milk. Thiazides do appear in human milk (see section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Lisinopril
Symptomatic Hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving lisinopril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (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 100mm 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 120mm Hg or lower. Maintenance doses should be reduced to 5mg or temporarily to 2.5mg if systolic blood pressure is 100mm Hg or lower. If hypotension persists (systolic blood pressure less than 90mm 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 <80ml/min), the initial lisinopril dosage should be adjusted according to the patient’s creatinine clearance and then as a function of the patient’s response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

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

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first few 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 177micromol/l and/or proteinuria exceeding 500mg/24h. If renal dysfunction develops during treatment with lisinopril (serum creatinine concentration exceeding 265micromol/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 section 4.5).

Lithium

The combination of lithium and lisinopril is generally not recommended (see section 4.5).
Pregnancy and lactation

**Pregnancy**

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Use of lisinopril is not recommended during breast-feeding.

**Hydrochlorothiazide**

**Renal impairment**

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30ml/min or below (i.e. moderate or severe renal insufficiency).

In patients with renal disease, thiazides may precipitate azotaemia. Cumulative effects of the drug may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy (see section 4.3).

**Hepatic impairment**

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see section 4.3).

**Metabolic and endocrine effects**

Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

**Electrolyte imbalance**

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea or vomiting.

Hypokalaemia may develop with the use of thiazide diuretics. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

**Anti-doping test**

Hydrochlorothiazide contained in this medication could produce a positive analytical result in an anti-doping test.

**Other**

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.
**Lisinopril/Hydrochlorothiazide combination**

**Renal impairment**

Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets should not be administered to patients with renal insufficiency (creatinine clearance <30ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.

In some patients with bilateral renal artery stenosis or 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, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when lisinopril has been given concomitantly with a diuretic. If this occurs during therapy, the combination should be discontinued. Reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

**Pregnancy**

Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets is not recommended during the first trimester of pregnancy (see section 4.6). If treatment is discontinued due to pregnancy, the prescriber should decide whether treatment of hypertension should be continued.

**Risk of hypokalaemia**

The combination of an ACE inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of kalaemia should be performed.

**Combination with lithium**

Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets is not recommended in association with lithium due to the potentiation of lithium toxicity (see section 4.5).

### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

**Lisinopril**

**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 minimized by discontinuing the diuretic prior to initiation of treatment with lisinopril (see section 4.4).

**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 ≥ 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 medicinal products (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

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

Hydrochlorothiazide
Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

Calcium salts
Increased serum calcium levels due to decreased excretion may occur when administered concurrently with thiazide diuretics.

Cardiac glycosides
Enhanced possibility of digitalis toxicity associated with thiazide induced hypokalaemia.

Cholestyramine resin and colestipol
May delay or decrease absorption of hydrochlorothiazide. Sulphonamide diuretics should be taken at least one hour before or four to six hours after these medications.

Non-depolarising muscle relaxants (e.g. tubocurarine chloride)
Effects of these agents may be potentiated by hydrochlorothiazide.

Drugs associated with torsades de pointes
Because of the risk of hypokalaemia, caution should be used when hydrochlorothiazide is coadministered with drugs associated with torsades de pointes, e.g. some anti-arrhythmics, some antipsychotics and other drugs known to induce torsades de pointes.

Clinical Chemistry
Hydrochlorothiazide may cause diagnostic interference of the bentiromide test. Thiazides may decrease serum PBI (Protein Bound Iodine) levels without signs of thyroid disturbance.

Lisinopril/Hydrochlorothiazide combination
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 risk of lithium toxicity with ACE inhibitors. The combination of lisinopril and hydrochlorothiazide with lithium is therefore not recommended and careful monitoring of serum lithium levels should be performed if the combination proves necessary.
Non-steroidal anti-inflammatory medicinal products
It has been described that non-steroidal anti-inflammatory medicinal products (NSAIDs) and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are, in principle, reversible. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated. Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. The administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics.

Serum potassium
The potassium-losing effect of thiazide diuretics is usually attenuated by the potassium-conserving effect of lisinopril. The use of potassium supplements, potassium-sparing agents or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If concomitant use of Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets and any of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

4.6 PREGNANCY AND LACTATION

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

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

Hydrochlorothiazide
Pregnancy
Hydrochlorothiazide, in cases of prolonged exposure during the third trimester of pregnancy, may cause foeto-placental ischaemia and risk of growth retardation. Moreover, rare cases of hypoglycaemia and thrombocytopenia in neonates have been reported in case of exposure near term. Hydrochlorothiazide can reduce plasma volume as well as the uteroplacental blood flow.

The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

Lactation
Hydrochlorothiazide is excreted in human milk. Thiazides during breast feeding by lactating mothers have been associated with a decrease or even suppression of the milk lactation. Hypersensitivity to sulphonamide-derived drugs, hypokalaemia and nuclear icterus may occur.
**Lisinopril/Hydrochlorothiazide combination**

**Pregnancy**

The use of Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets during pregnancy is not recommended. When pregnancy is detected Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets should be discontinued as soon as possible, unless it is considered life-saving for the mother.

If Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets is used during pregnancy, the patient should be apprized of the potential hazard to the foetus. In those rare cases where use during pregnancy is deemed essential, serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is detected, Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets should be discontinued unless it is considered life-saving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the foetus has sustained irreversible injury.

Infants whose mothers have taken Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets 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. There is no experience with the removal of hydrochlorothiazide, which also crosses the placenta, from the neonatal circulation.

**Lactation**

It is not known whether lisinopril is secreted in human milk; however, thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants, a decision should be made whether to discontinue breast-feeding or to discontinue Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets, taking into account the importance of the drug to the mother.

4.7 **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

When operating machinery or driving vehicles, it should be taken into account that dizziness, hypotension and tiredness may occur as adverse events of the combination.

4.8 **UNDESIRABLE EFFECTS**

**Lisinopril**

The following undesirable effects have been observed and reported during treatment with lisinopril and other ACE inhibitors with the following frequencies: Very common (≥10%), common (≥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

Hydrochlorothiazide

Infections and infestations:
sialadenitis

Blood and lymphatic system disorders:
leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression

Metabolism and nutrition disorders:
anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), increases in cholesterol and triglycerides

Psychiatric disorders:
restlessness, depression, sleep disturbances

Nervous system disorders:
loss of appetite, paraesthesia, light-headedness

Eye disorders:
xanthopsia, transient blurred vision

Ear and labyrinth disorders:
vertigo

Cardiac disorders:
postural hypotension, cardiac arrhythmias
Vascular disorders:
Necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders:
respiratory distress (including pneumonitis and pulmonary oedema)

Gastrointestinal disorders:
gastric irritation, diarrhoea, constipation, pancreatitis

Hepato-biliary disorders:
jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders:
photosensitivity reactions, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous
lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:
muscle spasm

Renal and urinary disorders:
renal dysfunction, interstitial nephritis

General disorders
fever, weakness

Lisinopril/Hydrochlorothiazide combination
In clinical studies, side effects have usually been mild and transient, and in most instances have not
required interruption of therapy. The side effects that have been observed have been limited to those
reported previously with lisinopril or hydrochlorothiazide.

One of the most common clinical side effects was dizziness, which generally responded to dosage
reduction and seldom required discontinuation of therapy.
Other side effects were headache, dry cough, fatigue and hypotension including orthostatic hypotension.
Less common were diarrhoea, nausea, vomiting, dry mouth, rash, gout, palpitations, chest discomfort,
muscle cramps and weakness, paraesthesia, asthenia and impotence.

Pancreatitis has been reported rarely with lisinopril and with hydrochlorothiazide and, therefore, is a
potential side effect of Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets.

Hypersensitivity/Angioneurotic Oedema
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely
(see section 4.4). In very rare cases, intestinal angioedema has been reported.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis,
myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leucocytosis, rash,
photosensitivity, or other dermatological manifestations.

Laboratory Test Findings
Laboratory side effects have rarely been of clinical importance. Occasional hyperglycaemia,
hyperuricaemia and hyper- or hypokalaemia have been noted. Usually minor and transient increases in
blood urea nitrogen and serum creatinine have been seen in patients without evidence of pre-existing
renal impairment. If such increases persist, they are usually reversible upon discontinuation of Lisinopril
and Hydrochlorothiazide 10mg/12.5mg Tablets. Bone marrow depression, manifest as anaemia and/or
thrombocytopenia and/or leucopenia has been reported. Agranulocytosis has been rarely reported. Small
decreases in haemoglobin and haematocrit have been reported frequently in hypertensive patients treated
with Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets but were rarely of clinical importance
unless another cause of anaemia co-existed. Rarely, elevations of liver enzymes and/or serum bilirubin
have occurred, but a causal relationship to Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets has
not been established.
4.9 OVERDOSE

**Lisinopril**

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

The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating lisinopril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

**Hydrochlorothiazide**

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

**Lisinopril/Hydrochlorothiazide combination**

No specific information is available on the treatment of overdosage with Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets. Treatment is symptomatic and supportive.

Therapy with Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets should be discontinued and the patient should be kept under very close supervision. Therapeutic measures depend on the nature and severity of the symptoms. Measures to prevent absorption and methods to speed elimination should be employed.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: ACE inhibitors and Diuretics
ATC code: C09BA03

**Lisinopril**

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.

**Hydrochlorothiazide**

Hydrochlorothiazide is a thiazide diuretic and an antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption and increases excretion of sodium and chloride in approximately equivalent amounts and, to a lesser extent, the excretion of potassium and magnesium. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effect of the thiazides is unknown. Thiazides do not usually affect normal blood pressure.

When combined with other antihypertensive agents, additive falls in blood pressure may occur.

Above a certain dose, thiazide diuretics reach a plateau in terms of therapeutic effect whereas adverse reactions continue to multiply. When treatment is ineffective, increasing the dose beyond recommended doses serves no useful purpose and often gives rise to adverse reactions.
Lisinopril and Hydrochlorothiazide combination

Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets is a fixed dose combination product containing lisinopril, an inhibitor of angiotensin converting enzyme (ACE) and hydrochlorothiazide, a thiazide diuretic. Both components have complementary modes of action and exert an additive antihypertensive effect.

5.2 PHARMACOKINETIC PROPERTIES

Lisinopril

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

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

Elimination
Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine. On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril in healthy subjects is approximately 50ml/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 30ml/min. In mild to moderate renal impairment (creatinine clearance 30-80ml/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 5-30ml/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 55ml/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.

Hydrochlorothiazide
Oral absorption of hydrochlorothiazide is relatively rapid. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the dose is eliminated unchanged within 24 hours. After oral hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Lisinopril/Hydrochlorothiazide combination
Concomitant multiple doses of lisinopril and hydrochlorothiazide has little or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.
5.3 PRECLINICAL SAFETY DATA

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

**Hydrochlorothiazide**
Animal studies performed during organogenesis with hydrochlorothiazide have not shown any teratogenic effect. Preclinical data reveal no other specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenicity.

**Lisinopril/Hydrochlorothiazide combination**
Lisinopril and hydrochlorothiazide are well established in medical use. Preclinical data is broadly consistent with clinical experience. For reproduction toxicity, see section 4.6.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Mannitol (E 421)
Calcium Hydrogen Phosphate Dihydrate
Maize Starch
Pregelatinised starch
Magnesium stearate
FD & C Blue No. 2 Aluminium Lake

6.2 INCOMPATIBILITIES
Not Applicable

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Store in the original carton in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER
PVC/PVDC/Al blisters in a carton.
Packs of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 500 tablets."Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.
Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20092/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/11/2009

10 DATE OF REVISION OF THE TEXT
03/11/2009
NAME OF THE MEDICINAL PRODUCT
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Tablet contains:
Lisinopril dihydrate equivalent to anhydrous Lisinopril 20mg and Hydrochlorothiazide 12.5mg
For a full list of excipients, see section 6.1

PHARMACEUTICAL FORM
Tablet
Yellow, hexagonal tablets, plain on both sides

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets is indicated in the management of mild to moderate hypertension in patients who have been stabilised on the individual components given in the same proportions.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Route of administration: Oral

Essential Hypertension
The usual dosage is one tablet, administered once daily. As with all other medication taken once daily, Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets should be taken at approximately the same time each day.
In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks at this dose level, the dose can be increased to two tablets administered once daily.

Use in the elderly
In clinical studies the efficacy and tolerability of lisinopril and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients. Lisinopril was equally effective in elderly (65 years or older) and non-elderly hypertensive patients. In elderly hypertensive patients, monotherapy with lisinopril was as effective in reducing diastolic blood pressure as monotherapy with either hydrochlorothiazide or atenolol. In clinical studies, age did not affect the tolerability of lisinopril.

Use in children
Safety and effectiveness in children have not been established.

Dosage in Renal Insufficiency
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30ml/min or below (i.e. moderate or severe renal insufficiency).

Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets is not to be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of >30 and <80ml/min, Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets may be used, but only after titration of the individual components.

Prior Diuretic Therapy
Symptomatic hypotension may occur following the initial dose of Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets; this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets. If this is not possible, treatment should be started with lisinopril alone, in a 2.5 mg dose.

CONTRAINDICATIONS
Lisinopril
Hypersensitivity to lisinopril, or any other angiotensin converting enzyme (ACE) inhibitor
History of angioedema associated with previous ACE inhibitor therapy
Hereditary or idiopathic angioedema
Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
Hydrochlorothiazide
- History of hypersensitivity to hydrochlorothiazide or other sulphonamide-derived drugs
- Severe renal impairment (creatinine clearance <30ml/min)
- Severe hepatic impairment
- Second or third trimesters of pregnancy (see section 4.6)
- Lactation (see section 4.6)

Lisinopril and Hydrochlorothiazide combination
- Hypersensitivity to lisinopril, hydrochlorothiazide or to any of the excipients
- Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets is contraindicated in patients with anuria or aortic stenosis or hyperkalaemia.

The use of Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets during pregnancy is not recommended. When pregnancy is detected Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets should be discontinued as soon as possible, unless it is considered life-saving for the mother.

Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets is contraindicated in lactating women who are breast-feeding infants. It is not known whether lisinopril is excreted in human milk. Thiazides do appear in human milk (see section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Lisinopril

Symptomatic Hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving lisinopril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (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 100mm 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 120mm Hg or lower. Maintenance doses should be reduced to 5mg or temporarily to 2.5mg if systolic blood pressure is 100mm Hg or lower. If hypotension persists (systolic blood pressure less than 90mm 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 <80ml/min), the initial lisinopril dosage should be adjusted according to the patient’s creatinine clearance and then as a function of the patient’s response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

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

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first few 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 177micromol/l and/or proteinuria exceeding 500mg/24h. If renal dysfunction develops during treatment with lisinopril (serum creatinine concentration exceeding 265micromol/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/Antesthesia
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 section 4.5).

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

Pregnancy and lactation
Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).
Use of lisinopril is not recommended during breast-feeding.

**Hydrochlorothiazide**

**Renal impairment**

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30ml/min or below (i.e. moderate or severe renal insufficiency). In patients with renal disease, thiazides may precipitate azotaemia. Cumulative effects of the drug may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy (see section 4.3).

**Hepatic impairment**

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see section 4.3).

**Metabolic and endocrine effects**

Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

**Electrolyte imbalance**

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea or vomiting.

Hypokalaemia may develop with the use of thiazide diuretics. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

**Anti-doping test**

Hydrochlorothiazide contained in this medication could produce a positive analytical result in an anti-doping test.

**Other**

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

**Lisinopril/Hydrochlorothiazide combination**

**Renal impairment**

Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets should not be administered to patients with renal insufficiency (creatinine clearance <80ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.
In some patients with bilateral renal artery stenosis or 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, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when lisinopril has been given concomitantly with a diuretic. If this occurs during therapy, the combination should be discontinued. Reinstatement of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

Pregnancy
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets is not recommended during the first trimester of pregnancy (see section 4.6). If treatment is discontinued due to pregnancy, the prescriber should decide whether treatment of hypertension should be continued.

Risk of hypokalaemia
The combination of an ACE inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of kalaemia should be performed.

Combination with lithium
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets is not recommended in association with lithium due to the potentiation of lithium toxicity (see section 4.5).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Lisinopril
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 minimized by discontinuing the diuretic prior to initiation of treatment with lisinopril (see section 4.4).

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 ≥ 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 medicinal products (insulins, oral hypoglycaemic agents) may cause an increased blood
glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to
occur during the first weeks of combined treatment and in patients with renal impairment.

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

Hydrochlorothiazide
Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant
laxatives
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

Calcium salts
Increased serum calcium levels due to decreased excretion may occur when administered concurrently
with thiazide diuretics.

Cardiac glycosides
Enhanced possibility of digitalis toxicity associated with thiazide induced hypokalaemia.

Cholestyramine resin and colestipol
May delay or decrease absorption of hydrochlorothiazide. Sulphonamide diuretics should be taken at
least one hour before or four to six hours after these medications.

Non-depolarising muscle relaxants (e.g. tubocurarine chloride)
Effects of these agents may be potentiated by hydrochlorothiazide.

Drugs associated with torsades de pointes
Because of the risk of hypokalaemia, caution should be used when hydrochlorothiazide is coadministered
with drugs associated with torsades de pointes, e.g. some anti-arrhythmics, some antipsychotics and other
drugs known to induce torsades de pointes.

Clinical Chemistry
Hydrochlorothiazide may cause diagnostic interference of the bentiromide test. Thiazides may decrease
serum PBI (Protein Bound Iodine) levels without signs of thyroid disturbance.

Lisinopril/Hydrochlorothiazide combination
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 risk of lithium toxicity with ACE inhibitors.
The combination of lisinopril and hydrochlorothiazide with lithium is therefore not recommended and
careful monitoring of serum lithium levels should be performed if the combination proves necessary.

Non-steroidal anti-inflammatory medicinal products
It has been described that non-steroidal anti-inflammatory medicinal products (NSAIDs) and ACE
inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may
decrease. These effects are, in principle, reversible. Rarely, acute renal failure may occur, particularly in
patients with compromised renal function such as the elderly or dehydrated. Chronic administration of
NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. The administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics.

Serum potassium
The potassium-losing effect of thiazide diuretics is usually attenuated by the potassium-conserving effect of lisinopril. The use of potassium supplements, potassium-sparing agents or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If concomitant use of Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets and any of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

4.6 PREGNANCY AND LACTATION

Lisinopril

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

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

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

Hydrochlorothiazide

Pregnancy
Hydrochlorothiazide, in cases of prolonged exposure during the third trimester of pregnancy, may cause foeto-placental ischaemia and risk of growth retardation. Moreover, rare cases of hypoglycaemia and thrombocytopenia in neonates have been reported in case of exposure near term. Hydrochlorothiazide can reduce plasma volume as well as the uteroplacental blood flow.

The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

Lactation
Hydrochlorothiazide is excreted in human milk. Thiazides during breast feeding by lactating mothers have been associated with a decrease or even suppression of the milk lactation. Hypersensitivity to sulphonamide-derived drugs, hypokalaemia and nuclear icterus may occur.

Lisinopril/Hydrochlorothiazide combination

Pregnancy
The use of Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets during pregnancy is not recommended. When pregnancy is detected Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets should be discontinued as soon as possible, unless it is considered life-saving for the mother.

If Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets is used during pregnancy, the patient should be apprised of the potential hazard to the foetus. In those rare cases where use during pregnancy is deemed essential, serial ultrasound examinations should be performed to assess the intraamniotic environment.
If oligohydramnios is detected, Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets should be discontinued unless it is considered life-saving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the foetus has sustained irreversible injury.

Infants whose mothers have taken Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets 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. There is no experience with the removal of hydrochlorothiazide, which also crosses the placenta, from the neonatal circulation.

**Lactation**

It is not known whether lisinopril is secreted in human milk; however, thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants, a decision should be made whether to discontinue breast-feeding or to discontinue Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets, taking into account the importance of the drug to the mother.

**4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

When operating machinery or driving vehicles, it should be taken into account that dizziness, hypotension and tiredness may occur as adverse events of the combination.

**4.8 UNDESIRABLE EFFECTS**

**Lisinopril**

The following undesirable effects have been observed and reported during treatment with lisinopril and other ACE inhibitors with the following frequencies: Very common (≥10%), common (≥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

**Hydrochlorothiazide**

Infections and infestations:
sialadenitis

Blood and lymphatic system disorders:
leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression

Metabolism and nutrition disorders:
anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), increases in cholesterol and triglycerides

Psychiatric disorders:
restlessness, depression, sleep disturbances

Nervous system disorders:
loss of appetite, paraesthesia, light-headedness

Eye disorders:
xanthopsia, transient blurred vision

Ear and labyrinth disorders:
vertigo

Cardiac disorders:
postural hypotension, cardiac arrhythmias

Vascular disorders:
Necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders:
respiratory distress (including pneumonitis and pulmonary oedema)

Gastrointestinal disorders:
gastric irritation, diarrhoea, constipation, pancreatitis

Hepato-biliary disorders:
jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders:
- photosensitivity reactions, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:
- muscle spasm

Renal and urinary disorders:
- renal dysfunction, interstitial nephritis

General disorders
- fever, weakness

Lisinopril/Hydrochlorothiazide combination
In clinical studies, side effects have usually been mild and transient, and in most instances have not required interruption of therapy. The side effects that have been observed have been limited to those reported previously with lisinopril or hydrochlorothiazide.

One of the most common clinical side effects was dizziness, which generally responded to dosage reduction and seldom required discontinuation of therapy.

Other side effects were headache, dry cough, fatigue and hypotension including orthostatic hypotension. Less common were diarrhoea, nausea, vomiting, dry mouth, rash, gout, palpitations, chest discomfort, muscle cramps and weakness, paraesthesia, asthenia and impotence.

Pancreatitis has been reported rarely with lisinopril and with hydrochlorothiazide and, therefore, is a potential side effect of Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets.

Hypersensitivity/Angioneurotic Oedema
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely (see section 4.4). In very rare cases, intestinal angioedema has been reported.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leucocytosis, rash, photosensitivity, or other dermatological manifestations.

Laboratory Test Findings
Laboratory side effects have rarely been of clinical importance. Occasional hyperglycaemia, hyperuricaemia and hyper- or hypokalaemia have been noted. Usually minor and transient increases in blood urea nitrogen and serum creatinine have been seen in patients without evidence of pre-existing renal impairment. If such increases persist, they are usually reversible upon discontinuation of Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets. Bone marrow depression, manifest as anaemia and/or thrombocytopenia and/or leucopenia has been reported. Agranulocytosis has been rarely reported. Small decreases in haemoglobin and haematocrit have been reported frequently in hypertensive patients treated with Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets but were rarely of clinical importance unless another cause of anaemia co-existed. Rarely, elevations of liver enzymes and/or serum bilirubin have occurred, but a causal relationship to Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets has not been established.

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

The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating lisinopril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.
Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Lisinopril/Hydrochlorothiazide combination

No specific information is available on the treatment of overdosage with Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets. Treatment is symptomatic and supportive.

Therapy with Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets should be discontinued and the patient should be kept under very close supervision. Therapeutic measures depend on the nature and severity of the symptoms. Measures to prevent absorption and methods to speed elimination should be employed.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: ACE inhibitors and Diuretics
ATC code: C09BA03

Lisinopril

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.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic and an antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption and increases excretion of sodium and chloride in approximately equivalent amounts and, to a lesser extent, the excretion of potassium and magnesium. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effect of the thiazides is unknown. Thiazides do not usually affect normal blood pressure. When combined with other antihypertensive agents, additive falls in blood pressure may occur.

Above a certain dose, thiazide diuretics reach a plateau in terms of therapeutic effect whereas adverse reactions continue to multiply. When treatment is ineffective, increasing the dose beyond recommended doses serves no useful purpose and often gives rise to adverse reactions.

Lisinopril/Hydrochlorothiazide combination

Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets is a fixed dose combination product containing lisinopril, an inhibitor of angiotensin converting enzyme (ACE) and hydrochlorothiazide, a thiazide diuretic. Both components have complementary modes of action and exert an additive antihypertensive effect.

5.2 PHARMACOKINETIC PROPERTIES

Lisinopril

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

Absorption

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25% with inter-patient variability of 6-60% over the dose range studied (5-80mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure. Lisinopril absorption is not affected by the presence of food.
Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets

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

**Elimination**
Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine. On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril in healthy subjects is approximately 50ml/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 30ml/min. In mild to moderate renal impairment (creatinine clearance 30-80ml/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 5-30ml/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 55ml/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.

**Hydrochlorothiazide**
Oral absorption of hydrochlorothiazide is relatively rapid. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the dose is eliminated unchanged within 24 hours. After oral hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

**Lisinopril/Hydrochlorothiazide combination**
Concomitant multiple doses of lisinopril and hydrochlorothiazide has little or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

### 5.3 PRECLINICAL SAFETY DATA

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

**Hydrochlorothiazide**
Animal studies performed during organogenesis with hydrochlorothiazide have not shown any teratogenic effect. Preclinical data reveal no other specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.
**Lisinopril/Hydrochlorothiazide combination**
Lisinopril and hydrochlorothiazide are well established in medical use. Preclinical data is broadly consistent with clinical experience. For reproduction toxicity, see section 4.6.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **LIST OF EXCIPIENTS**
- Mannitol (E 421)
- Calcium Hydrogen Phosphate Dihydrate
- Maize Starch
- Pregelatinised starch
- Magnesium stearate
- Yellow Iron Oxide

6.2 **INCOMPATIBILITIES**
Not Applicable

6.3 **SHELF LIFE**
2 years.

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**
Store below 30°C. Store in the original carton in order to protect from light.

6.5 **NATURE AND CONTENTS OF CONTAINER**
PVC/PVDC/Al blisters in a carton.
Packs of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 500 tablets.
Not all pack sizes may be marketed.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**
No special requirements.
Any unused product or waste material should be disposed off in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 20092/0028

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
03/11/2009

10 **DATE OF REVISION OF THE TEXT**
03/11/2009
UKPAR Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets

PATIENT INFORMATION LEAFLET
Lisinopril and Hydrochlorothiazide
10mg/12.5mg TABLETS
and
Lisinopril and Hydrochlorothiazide
20mg/12.5mg TABLETS

Lisinopril and Hydrochlorothiazide

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

In This Leaflet:
1. What Lisinopril and Hydrochlorothiazide Tablets is and what it is used for
2. Before you take Lisinopril and Hydrochlorothiazide Tablets
3. How to take Lisinopril and Hydrochlorothiazide Tablets
4. Possible side effects
5. How to store Lisinopril and Hydrochlorothiazide Tablets
6. Further information

1. WHAT LISINOPRIL AND HYDROCHLOROTHIAZIDE TABLETS IS AND WHAT IT IS USED FOR.
Lisinopril belongs to a group of medicines called 'ACE Inhibitors'. These work by widening blood vessels which makes it easier for the heart to pump blood through them, to all parts of the body.
This helps to reduce blood pressure. Hydrochlorothiazide belongs to a group of medicines called water tablets. These work by increasing the amount of urine made by the kidneys. Each reduces blood pressure in a different way.
These tablets are to treat high blood pressure.

2. BEFORE YOU TAKE LISINOPRIL AND HYDROCHLOROTHIAZIDE TABLETS
Do not take Lisinopril and Hydrochlorothiazide Tablets If you
- are allergic (hypersensitive) to lisinopril, hydrochlorothiazide or to certain water tablets, those similar to sulphonamides (a type of antibiotic) or any other of the ingredients of Lisinopril and Hydrochlorothiazide Tablets
- have been treated before with a medicine in the same group of drugs, ACE Inhibitors, and have had allergic reactions involving difficulty with swallowing or breathing, swelling of the hands, feet or ankles, face, lips, tongue or throat or if you or a member of your family has had a similar reaction for any other reason
- are more than 3 months pregnant. (It is also best to avoid Lisinopril and Hydrochlorothiazide Tablets in early pregnancy – see pregnancy section)
- are breast feeding or planning to breast feed
- have a narrowing of the aortic valve
- are not passing urine or have other kidney problems that your doctor does not know about
- are suffering from liver problems
- have high levels of potassium in your blood
- are under 18 years of age

If you think that any of these apply to you, do not take the tablets. Tell your doctor and follow the advice given.
These tablets are only for you, they must not be given to anyone else.

Take special care with Lisinopril and Hydrochlorothiazide Tablets If you
- have narrowing of the renal artery (renal artery stenosis) or an increase in the thickness of the heart muscle (hypertrophic cardiomyopathy, HCM)
- have any other heart problems e.g. angina
- have problems with liver or kidneys or are undergoing dialysis
- are on a low-salt diet and you use potassium containing salt substitutes or supplements
- suffer from diarrhoea or vomiting
- are going to have desensitisation treatment (e.g. treatment to reduce the effects of an allergy to bee or wasp stings)
- have diabetes, as you may need a different dose of your antidiabetic medicines
- have or have had the inflammatory condition known as lupus (systemic lupus erythematosus, SLE) which is caused by an autoimmune disease
- go into hospital tell the medical staff, especially the anaesthetist (if you are having an operation) that you are taking these tablets. You should also tell your dentist before you have an anaesthetic for a dental procedure
- you must tell your doctor if you think you are (or might become) pregnant. Lisinopril and Hydrochlorothiazide Tablets is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section)

Check with your doctor, if you are not sure.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular tell your doctor or pharmacist if you are taking
- water tablets, as these may cause an excessive fall in your blood pressure
- other treatment for high blood pressure, as these may further reduce your blood pressure
- indomethacin (for arthritis or muscle pains), as this may reduce the effect of these tablets
- lithium (for depression), as taking these tablets may cause the level of lithium in your blood to rise
- drugs to treat depression, psychosis and anaesthetics as these may further reduce your blood pressure
- sympathomimetics, drugs that affect a part of the nervous system that acts as a control system within your body, as they may reduce the blood pressure lowering effect of taking these tablets
- antidiabetics, as taking these tablets may increase chances of low blood sugar
- digitalis or digoxin preparations: Digitalis toxicity may be enhanced because of low potassium levels in the blood
- muscle relaxants, for example tubocurarine chloride, as their effects may be increased by these tablets
Pregnancy and breast-feeding

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Lisinopril and Hydrochlorothiazide Tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Lisinopril and Hydrochlorothiazide Tablets. Lisinopril and Hydrochlorothiazide Tablets is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Lisinopril and Hydrochlorothiazide Tablets is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machinery
When driving or using any tools or machines take care as these tablets may cause dizziness, low blood pressure and tiredness.

3. HOW TO TAKE LISINOPRIL AND HYDROCHLOROTHIAZIDE TABLETS
Always take Lisinopril and Hydrochlorothiazide Tablets as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
You must keep taking Lisinopril and Hydrochlorothiazide Tablets, even if you are feeling well, because regular treatment is most effective. The dose you take will depend on your condition and whether you are taking any other medicines.
- The usual dose is one or two tablets once a day, taken with a glass of water
- Try to take your tablet(s) at the same time each day. Many patients prefer to take them in the morning so that the effects of the water tablet (passing more water than usual) occur during the daytime
- If you are taking these tablets for the first time you may feel light-headed or dizzy for a short time and it may help to sit or lie down. This is unlikely to happen when you are taking the tablets regularly.
If you are worried, contact your doctor

If you take more Lisinopril and Hydrochlorothiazide Tablets than you should
If you take more than your normal dose, contact your doctor or nearest hospital.

If you forget to take Lisinopril and Hydrochlorothiazide Tablets
If you do forget to take a dose of your medicine at the correct time, just carry on with the next dose when it is due. Do not take a double dose to make up for a forgotten dose.

If you stop taking Lisinopril and Hydrochlorothiazide Tablets
Always check with your doctor before you stop taking this medicine.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Lisinopril and Hydrochlorothiazide Tablets can cause side effects, although not everybody gets them. Do not be alarmed by this list - you may not have any of them.
You should stop taking these tablets and contact your doctor immediately in any of the following situations: if you
- develop difficulty in breathing with or without swelling of the face, lips, tongue and/or throat
- develop swelling of the face, lips, tongue, and/or throat which may cause difficulty in swallowing
- develop severe itching of the skin (with raised lumps)

**Lisinopril**

Common: affecting at least or more than 1 in 100 patients treated but less than 1 in 10 patients treated
- dizziness
- headache
- low blood pressure which is felt on standing
- diarrhoea
- vomiting
- cough
- kidney problems

Uncommon: affecting at least or more than 1 in 1000 patients but less than 1 in 100 patients
- mood alterations
- tingling or numbness in the hands or feet
- feeling of spinning sensation
- taste disturbance
- sleep disturbances
- heart attack
- rapid and irregular heartbeat
- poor blood circulation which makes the toes and fingers numb and pale
- running nose
- feeling sick
- abdominal pain and indigestion
- rash
- itching
- loss of sexual performance in man
- fatigue
- feeling weakness
- raised creatinine and urea blood levels, increases in liver enzymes, low blood levels of potassium

Rare: affecting at least or more than 1 in 10,000 patients but less than 1 in 1000 patients
- low haemoglobin levels
- mental confusion
- dry mouth
- a serious allergic reaction with swelling of face, lips, tongue
- inflammation of mouth, and/or larynx
- hives
- hair loss
- reddening of the skin
- kidney failure
- breast enlargement in males
- high levels of bilirubin in the blood
- low blood levels of sodium which can cause tiredness and confusion, muscle twitching, fits and coma

Very rare: affecting less than 1 in 10,000 patients
- bone marrow depression
- reduction in red blood cells
- reduction in blood platelets which increases risk of bleeding or bruising
- severe reduction in number of white blood cells which makes infection more likely
- abnormal breakdown of red blood cells
- lymph disorders
- autoimmune disease
- low blood sugar levels
- shortness of breath
- swollen sinuses
- allergic lung disorder or accumulation of eosinophils in the lungs
- pancreas inflammation
- intestinal swellings
- jaundice due to impaired excretion of bile pigment
- profuse sweating
- a very rare but serious blistering of the skin
- rash involving reddening, swelling and peeling of the skin if it resemble severe burns
- a severe and widespread reddening of the skin with blistering
- a painful reddening of the skin with lumps and blisters

With **Hydrochlorothiazide** few patients have reported the following
- loss of appetite
- stomach upset
- nausea
- vomiting
- stomach cramps
- constipation
- jaundice as yellowing of the skin and/or whites of the eyes
- an inflamed pancreas marked by pain in the abdomen and back
- swelling of the salivary glands
- vertigo (spinning sensation)
- pins and needles
- headache
- visual changes which can make objects appear yellow
- anaemia marked by unusual tiredness and a loss of colour in the linings of the eyes and skin
- other blood disorders which can result in fever
- sore throat or prolonged bleeding after injury
- increased skin sensitivity to sunlight
- purplish or reddish-brown marks on the skin
- fever
- hives or a nettle-like rash
- inflammation of blood vessels
- breathing problems due to inflamed or swollen lungs
- allergic reactions marked by rash, hives, or difficulties in breathing or swallowing
- blistering or peeling of the skin, mouth, eyes or genitals
- changes in the levels of certain chemicals in the blood and urine which are usually detected by blood and urine tests
- kidney problems
- muscle spasm
- weakness
- restlessness
- blurred vision

It is possible that your doctor may occasionally take blood samples to check whether Lisinopril and Hydrochlorothiazide Tablets have had any effect on your blood for e.g. haemoglobin, blood count.

Sometimes these changes may show themselves as tiredness or sore throat, unusual bruising or bleeding.

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

5 HOW TO STORE LISINOPRIL AND HYDROCHLOROTHIAZIDE TABLETS
Keep out of the reach and sight of children.
Do not use Lisinopril and Hydrochlorothiazide Tablets after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Store below 30°C. Store in the original carton to protect from light.
Medicines should not be disposed of via waste water 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 and Hydrochlorothiazide Tablets contains
Lisinopril and Hydrochlorothiazide 10mg/12.5 mg Tablets contains lisinopril dihydrate equivalent to 10mg of lisinopril and 12.5mg of hydrochlorothiazide.
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets contains lisinopril dihydrate equivalent to 20mg of lisinopril and 12.5mg of hydrochlorothiazide.
The active substances are lisinopril dihydrate and hydrochlorothiazide.
The other ingredients are mannitol (E 421), calcium hydrogen phosphate dihydrate, maize starch, pregelatinised starch, magnesium stearate.
Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets also contain FD & C Blue No. 2 Aluminium Lake
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets also contain Yellow Iron Oxide.
What Lisinopril and Hydrochlorothiazide Tablets look like and the contents of the pack
Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets are blue, hexagonal tablets, without any markings.
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets are yellow, hexagonal tablets, without any markings.
Lisinopril and Hydrochlorothiazide Tablets are available in packs of 1, 10, 14, 15, 20, 26, 30, 32, 40, 50, 56, 60, 70, 80, 84, 90, 98, 100, 200, 250, 400, 500 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Lupin (Europe) Limited,
Victoria Court,
Bexton Road,
Knutford,
Cheshire, WA16 OPF
United Kingdom.

Date of preparation: June 2009
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UKPAR Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets
PL 20092/0027-8

Each tablet contains: Lisinopril dihydrate equivalent to 20 mg lisinopril and 12.5 mg hydrochlorothiazide.

Dosage: For oral use. Read enclosed leaflet before use.

Storage: Store below 30°C. Store in the original container in order to protect from light.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Lisinopril & Hydrochlorothiazide
20 mg / 12.5 mg Tablets
Lisinopril and Hydrochlorothiazide
28 Tablets
Lupin (Europe) Ltd.

Lisinopril & Hydrochlorothiazide
20 mg / 12.5 mg Tablets
28 Tablets
Lupin (Europe) Limited, Victoria Court, Buxton Road,
Knutsford, Cheshire WA16 0PF, UK
PL 20092/0027 Code No. GO/34/RG/06/854

Lisinopril & Hydrochlorothiazide
20 mg / 12.5 mg Tablets
28 Tablets

Please affix dispensary label here

8 901107001636
UKPAR Lisinopril and Hydrochlorothiazide 10mg/12.5mg Tablets
Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets

SUN
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Lisinopril and Hydrochlorothiazide 20mg/12.5mg Tablets

PL 20092/0027-8