Lisinopril 5mg, 10mg and 20mg Tablets

PL 20075/0131-3

UKPAR

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Lisinopril 5mg, 10mg and 20mg Tablets

PL 20075/0131-3

LAY SUMMARY

The MHRA granted Accord Healthcare Limited Marketing Authorisations (licences) for the medicinal products Lisinopril 5mg, 10mg and 20mg Tablets (PL 20075/0131-3) on 18th September 2008. These products are prescription only medicines.

Lisinopril tablets are used:

1. in the treatment of high blood pressure (hypertension)
2. in patients whose heart is unable to pump properly (heart failure)
3. after an acute heart attack
4. to treat kidney problems due to diabetes in hypertensive patients

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

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisation for the medicinal products Lisinopril 5mg, 10mg and 20mg Tablets (PL 20075/0131-3) to Accord Healthcare Limited on 18th September 2008. These products are Prescription Only Medicines (POM).

The application was submitted as simple abridged application according to article 10.1(c) of Directive 2001/83/EC, cross-referring to Lisinopril 5mg, 10mg and 20mg Tablets (PL 19156/0024-6) approved to Accord Healthcare Limited.

No new data was submitted nor was it necessary for these simple applications, as the data is identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated.

Lisinopril tablets belong to a group of medicines called ACE inhibitors. ACE is short for Angiotensin-Converting Enzyme. ACE inhibitors cause the body to produce less angiotensin (a hormone which tightens blood vessels and increase blood pressure), resulting in a reduction in pressure inside blood vessels and an improvement in heart function.
1. INTRODUCTION

This is a simple abridged application for Lisinopril 5mg, 10mg and 20mg Tablets submitted under Article 10 (c) of Directive 2001/83/EC. The proposed MA holder is Accord Healthcare Limited, Sage House, 319 Pinner Road, Harrow, Middlesex, HA1 4HF, UK.

These applications refer to marketing authorisations granted to PSI (Lisinopril 5mg, 10mg and 20mg Tablets, PL 19156/0024-6).

A letter of access has been provided from PSI dated 9TH February 2008 authorising the MHRA to refer to PL 19156/0024-6 as the reference for the purpose of these informed consent applications. Accord has also confirmed that they are in possession of all the necessary data to support this application including the quality dossier.

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the product is identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Lisinopril 5mg, 10mg and 20mg Tablets. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains lisinopril equivalent to 5mg, 10mg and 20mg anhydrous lisinopril respectively.

The products will be packaged into PVC/PVDC/aluminium blisters. The packagings are identical to the blister packaging for the reference product. The pack sizes are also identical to the reference product.
The respective SPC have indicated that Lisinopril 5mg, 10mg and 20mg Tablets will be packed into blister packs with pack sizes 14, 28, 30 or 98 in transparent PVC/PVDC/Aluminium blisters only as restricted for Prescription only medicines.

The same pack sizes are stated in the reference product. The proposed shelf life of 2 years is identical to the reference product. The proposed storage conditions are also identical to the reference product.

2.3 Legal status

The products are Prescription only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is Accord Healthcare Limited, 319 Pinner Road, North Harrow, Middlesex HA1 4HF, UK.

The QP responsible for pharmacovigilance is stated and a CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with that registered for the cross-reference product and evidence of GMP compliance has been provided. A flow diagram showing the sequence and activities of the different sites involved in the manufacturing process has been provided.

2.6 Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification

The proposed finished product specification is in line with the details registered for the cross-reference products.

2.9 Drug substance specification

The proposed drug substance specification conformed to current Ph Eur monograph for lisinopril as consistent with that of the reference product.

Current Ph Eur certificates of suitability for all three drug substance manufacturer have been provided to support the sources of active substance. These manufacturers are in line with the reference product.
2.10 TSE Compliance

The applicant has stated in the cover letter that no excipients of human or animal origin have been used.

2.11 Bioequivalence / Bioavailability

No bioavailability and bioequivalence data are required to support this informed consent application.

3. EXPERT REPORTS

The applicant has included detailed expert reports of the application. Signed declarations and copies of the experts’ CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product name. The appearance of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SmPCs are consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/BLISTER

PIL

The patient information leaflet has been prepared in-line with the details registered for the cross-reference products.

The result of user testing has been provided.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The data submitted with the application is acceptable. Marketing Authorisations should be granted.
PRECLINICAL ASSESSMENT

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

No new clinical data have been supplied and none are required.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

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

EFFICACY

Lisinopril is a well known drug and has been used for many years. These applications are identical to previously granted applications for Lisinopril 5mg, 10mg and 20mg Tablets (PL 19156/0024-6).

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the product is identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with Lisinopril is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 05/03/2008</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 26/03/2008.</td>
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<td>3</td>
<td>Following assessment of the application the MHRA requested further information on 28/05/2008 and 07/08/2008</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 24/06/2008 and 08/09/2008</td>
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<tr>
<td>7</td>
<td>The application was determined on 18/09/2008</td>
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## STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
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Lisinopril 5mg, 10mg and 20mg Tablets

PL 20075/0131-3

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lisinopril 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains lisinopril dihydrate equivalent to 5 mg anhydrous lisinopril.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablets.
5 mg tablets are white, round biconvex tablets with embossing “5” on one side and breakline on the other side.
The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of hypertension.

Heart Failure
Treatment of symptomatic heart failure.

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

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

4.2 Posology and method of administration
Lisinopril tablets should be administered orally in a single daily dose. As with all other medication taken once daily, Lisinopril tablets should be taken at approximately the same time each day. The absorption of Lisinopril tablets is not affected by food.
The dose should be individualised according to patient profile and blood pressure response (see section 4.4)

Hypertension
Lisinopril tablets may be used as monotherapy or in combination with other classes of antihypertensive medicinal products.

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

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

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

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

Table 1 Dosage adjustment in renal impairment.

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Starting Dose (mg/day)</th>
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<tbody>
<tr>
<td>Less than 10 ml/min (including patients on dialysis)</td>
<td>2.5 mg*</td>
</tr>
<tr>
<td>10-30 ml/min</td>
<td>2.5-5 mg</td>
</tr>
<tr>
<td>31-80 ml/min</td>
<td>5-10 mg</td>
</tr>
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</table>

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure
In patients with symptomatic heart failure, Lisinopril tablets should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. Lisinopril tablets may be initiated at a starting dose of 2.5 mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of Lisinopril tablets should be increased:
- By increments of no greater than 10 mg
- At intervals of no less than 2 weeks
To the highest dose tolerated by the patient up to a maximum of 35 mg once daily. Dose adjustment should be based on the clinical response of individual patients. Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Lisinopril tablets. Renal function and serum potassium should be monitored (see section 4.4).

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

Starting dose (first 3 days after infarction)
Treatment with Lisinopril tablets may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Lisinopril tablets is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4). In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril tablets dosage should be adjusted according to the patient’s creatinine clearance (see Table 1).
Maintenance dose
The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) Lisinopril tablets should be withdrawn. Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Lisinopril tablets (see section 4.2).

Renal Complications of Diabetes Mellitus
In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg Lisinopril tablets once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg. In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril tablets dosage should be adjusted according to the patient’s creatinine clearance (see Table 1).

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

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

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

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

4.4 Special warnings and precautions for use
Symptomatic Hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Lisinopril tablets, 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 tablets. 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 tablets may be necessary.
Hypotension In Acute Myocardial Infarction
Treatment with Lisinopril tablets must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or those in cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg for more than 1 hour) then Lisinopril tablets should be withdrawn.

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

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

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

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

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

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 tablets. This may occur at any time during therapy. In such cases, Lisinopril tablets 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 4.3 Contraindications).

**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 or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Lisinopril tablets who develop jaundice or marked elevations of hepatic enzymes should discontinue Lisinopril tablets 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 tablets 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 tablets 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 tablets 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 tablets 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 tablets. 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 tablets is generally not recommended (see section 4.5).

Pregnancy and lactation
Lisinopril should not be used during the first trimester of pregnancy. Lisinopril tablets is contraindicated in the second and third trimesters of pregnancy (see section 4.3). When pregnancy is detected, lisinopril treatment should be discontinued as soon as possible (see section 4.6).
Use of lisinopril is not recommended during breast-feeding.

4.5 Interaction with other medicinal products and other forms of interaction

Hypersensitivity/Angioedema
When a diuretic is added to the therapy of a patient receiving Lisinopril tablets 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 tablets is added. The possibility of symptomatic hypotension with Lisinopril tablets can be minimised by discontinuing the diuretic prior to initiation of treatment with Lisinopril tablets (see section 4.2 and 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 tablets 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 tablets 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 tablets. 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 tablets may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

4.6 Pregnancy and lactation

Pregnancy
Lisinopril tablets should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester toxicity exposure have not appeared to manifest malformations consistent with human foetotoxicity as described below. Lisinopril tablets is contraindicated during the second and third trimester of pregnancy (see section 4.3).

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia, see also section 5.3). Should exposure to Lisinopril tablets have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended. Infants whose mothers have taken Lisinopril tablets should be closely observed for hypotension, oliguria and hyperkalaemia. Lisinopril tablets, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

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

4.7 Effects on ability to drive and use machines
When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

4.8 Undesirable effects
The following undesirable effects have been observed and reported during treatment with Lisinopril tablets 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.

4.9 Overdose
Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating Lisinopril tablets (e.g., emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril tablets 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.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03
Lisinopril tablets is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

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

The effect of Lisinopril tablets on mortality and morbidity in heart failure has been studied by comparing a high dose (32.5 mg or 35 mg once daily) with a low dose (2.5 mg or 5 mg once daily). In a study of 3164 patients, with a median follow up period of 46 months for surviving patients, high dose Lisinopril tablets produced a 12% risk reduction in the combined endpoint of all-cause mortality and all-cause hospitalisation (p = 0.002) and an 8% risk reduction in all-cause mortality and cardiovascular hospitalisation (p = 0.036) compared with low dose. Risk reductions for all-cause mortality (8%; p = 0.128) and cardiovascular mortality (10%; p = 0.073) were observed. In a post-hoc analysis, the number of hospitalisations for heart failure was reduced by 24% (p=0.002) in patients treated with high-dose Lisinopril tablets compared with low dose. Symptomatic benefits were similar in patients treated with high and low doses of Lisinopril tablets.

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

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

In a double-blind, randomised, multicentre trial which compared Lisinopril tablets with a calcium channel blocker in 335 hypertensive Type 2 diabetes mellitus subjects with incipient nephropathy characterised by microalbuminuria, Lisinopril tablets 10 mg to 20 mg administered once daily for 12 months, reduced systolic/diastolic blood pressure by 13/10 mmHg and urinary albumin excretion rate by 40%. When compared with the calcium channel blocker, which produced a similar reduction in blood pressure, those treated with Lisinopril tablets showed a significantly greater reduction in urinary albumin excretion rate, providing evidence that the ACE inhibitory action of Lisinopril tablets reduced microalbuminuria by a direct mechanism on renal tissues in addition to its blood pressure lowering effect.
Lisinopril treatment does not affect glycaemic control as shown by a lack of significant effect on levels of glycated haemoglobin (HbA1c).

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

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

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

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

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

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Calcium hydrogen phosphate dihydrate
Maize starch
Starch, pregelatinised
Magnesium stearate
Silica, colloidal anhydrous

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Carton containing 14, 28, 30 or 98 tablets in transparent PVC/PVDC/Aluminium blisters. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The easiest way to break the tablet is illustrated below:
- place the tablet with the score on top
- place thumb and index of the same hand on each side of the score line and press as shown on the drawing.

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

7 MARKETING AUTHORISATION HOLDER
Accord Healthcare Limited
319 Pinner Road
North Harrow
Middlesex HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20075/0131

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/09/2008

10 DATE OF REVISION OF THE TEXT
18/09/2008
1 NAME OF THE MEDICINAL PRODUCT
Lisinopril 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains lisinopril dihydrate equivalent to 10 mg anhydrous lisinopril.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablets.
10 mg tablets are white, round biconvex tablets with embossing “10” on one side and
breakline on the other side.
The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of hypertension.

Heart Failure
Treatment of symptomatic heart failure.

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

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

4.2 Posology and method of administration
Lisinopril tablets should be administered orally in a single daily dose. As with all other
medication taken once daily, Lisinopril tablets should be taken at approximately the same time
each day. The absorption of Lisinopril tablets is not affected by food.
The dose should be individualised according to patient profile and blood pressure response
(see section 4.4)

Hypertension
Lisinopril tablets may be used as monotherapy or in combination with other classes of
antihypertensive medicinal products.

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

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

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

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

Table 2 Dosage adjustment in renal impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Starting Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 10 ml/min (including patients on dialysis)</td>
<td>2.5 mg*</td>
</tr>
<tr>
<td>10-30 ml/min</td>
<td>2.5-5 mg</td>
</tr>
<tr>
<td>31-80 ml/min</td>
<td>5-10 mg</td>
</tr>
</tbody>
</table>

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure
In patients with symptomatic heart failure, Lisinopril tablets should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. Lisinopril tablets may be initiated at a starting dose of 2.5 mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of Lisinopril tablets should be increased:
By increments of no greater than 10 mg
At intervals of no less than 2 weeks
To the highest dose tolerated by the patient up to a maximum of 35 mg once daily.
Dose adjustment should be based on the clinical response of individual patients. Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Lisinopril tablets. Renal function and serum potassium should be monitored (see section 4.4).

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

Starting dose (first 3 days after infarction)
Treatment with Lisinopril tablets may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Lisinopril tablets is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4).
In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril tablets dosage should be adjusted according to the patient’s creatinine clearance (see Table 1).

Maintenance dose
The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) Lisinopril tablets should be withdrawn.
Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Lisinopril tablets (see section 4.2).

Renal Complications of Diabetes Mellitus
In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg Lisinopril tablets once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg. In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril tablets dosage should be adjusted according to the patient’s creatinine clearance (see Table 1).

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

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

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

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

4.4 Special warnings and precautions for use
Symptomatic Hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Lisinopril tablets, 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 tablets. 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 tablets may be necessary.

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

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

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

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

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

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

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 tablets. This may occur at any time during therapy. In such cases, Lisinopril tablets 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 4.3 Contraindications).
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 or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Lisinopril tablets who develop jaundice or marked elevations of hepatic enzymes should discontinue Lisinopril tablets 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 tablets 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 tablets 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 tablets 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 tablets 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 tablets. 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 tablets is generally not recommended (see section 4.5).

**Pregnancy and lactation**

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

### 4.5 Interaction with other medicinal products and other forms of interaction

When a diuretic is added to the therapy of a patient receiving Lisinopril tablets 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 tablets is added. The possibility of symptomatic hypotension with Lisinopril tablets can be minimised by discontinuing the diuretic prior to initiation of treatment with Lisinopril tablets (see section 4.2 and 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 tablets 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 tablets 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 tablets. 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 tablets may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

4.6 Pregnancy and lactation

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

Lisinopril tablets is contraindicated during the second and third trimester of pregnancy (see section 4.3). Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia, see also section 5.3).

Should exposure to Lisinopril tablets have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended. Infants whose mothers have taken Lisinopril tablets should be closely observed for hypotension, oliguria and hyperkalaemia. Lisinopril tablets, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

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

4.7 Effects on ability to drive and use machines
When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

4.8 Undesirable effects
The following undesirable effects have been observed and reported during treatment with Lisinopril tablets 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.

4.9 Overdose
Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating Lisinopril tablets (e.g., emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril tablets 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.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03
Lisinopril tablets is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.
Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.
Whilst the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.
The effect of Lisinopril tablets on mortality and morbidity in heart failure has been studied by comparing a high dose (32.5 mg or 35 mg once daily) with a low dose (2.5 mg or 5 mg once daily). In a study of 3164 patients, with a median follow up period of 46 months for surviving patients, high dose Lisinopril tablets produced a 12% risk reduction in the combined endpoint of all-cause mortality and all-cause hospitalisation (p = 0.002) and an 8% risk reduction in all-cause mortality and cardiovascular hospitalisation (p = 0.036) compared with low dose. Risk reductions for all-cause mortality (8%; p = 0.128) and cardiovascular mortality (10%; p = 0.073) were observed. In a post-hoc analysis, the number of hospitalisations for heart failure was reduced by 24% (p=0.002) in patients treated with high-dose Lisinopril tablets compared with low dose. Symptomatic benefits were similar in patients treated with high and low doses of Lisinopril tablets.
The results of the study showed that the overall adverse event profiles for patients treated with high or low dose Lisinopril tablets were similar in both nature and number. Predictable events resulting from ACE inhibition, such as hypotension or altered renal function, were manageable and rarely led to treatment withdrawal. Cough was less frequent in patients treated with high dose Lisinopril tablets compared with low dose.
In the GISSI-3 trial, which used a 2x2 factorial design to compare the effects of Lisinopril tablets and glyceryl trinitrate given alone or in combination for 6 weeks versus control in 19,394, patients who were administered the treatment within 24 hours of an acute myocardial infarction, Lisinopril tablets produced a statistically significant risk reduction in mortality of 11% versus control (2p = 0.03). The risk reduction with glyceryl trinitrate was not significant but the combination of Lisinopril tablets and glyceryl trinitrate produced a significant risk reduction in mortality of 17% versus control (2p = 0.02). In the sub-groups of elderly (age > 70 years) and females, pre-defined as patients at high risk of mortality, significant benefit was observed for a combined endpoint of mortality and cardiac function. The combined endpoint for all patients, as well as the high-risk sub-groups, at 6 months also showed significant benefit for those treated with Lisinopril tablets or Lisinopril tablets plus glyceryl trinitrate for 6 weeks, indicating a prevention effect for Lisinopril tablets. As would be expected from any vasodilator treatment, increased incidences of hypotension and renal dysfunction were associated with Lisinopril tablets treatment but these were not associated with a proportional increase in mortality.
In a double-blind, randomised, multicentre trial which compared Lisinopril tablets with a calcium channel blocker in 335 hypertensive Type 2 diabetes mellitus subjects with incipient nephropathy characterised by microalbuminuria, Lisinopril tablets 10 mg to 20 mg administered once daily for 12 months, reduced systolic/diastolic blood pressure by 13/10 mmHg and urinary albumin excretion rate by 40%. When compared with the calcium channel blocker, which produced a similar reduction in blood pressure, those treated with Lisinopril tablets showed a significantly greater reduction in urinary albumin excretion rate, providing evidence that the ACE inhibitory action of Lisinopril tablets reduced microalbuminuria by a direct mechanism on renal tissues in addition to its blood pressure lowering effect.
Lisinopril treatment does not affect glycaemic control as shown by a lack of significant effect on levels of glycated haemoglobin (HbA1c).
5.2 Pharmacokinetic properties
Lisinopril is an orally active non-sulphydryl-containing ACE inhibitor.

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

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

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

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

Renal impairment
Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. In mild to moderate renal impairment (creatinine clearance 30-80 ml/min) mean AUC was increased by 13% only, while a 4.5-fold increase in mean AUC was observed in severe renal impairment (creatinine clearance 5-30 ml/min). Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55 ml/min.

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

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

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

6.1 List of excipients
Mannitol
Calcium hydrogen phosphate dihydrate
Maize starch
Starch, pregelatinised
Magnesium stearate
Silica, colloidal anhydrous

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Carton containing 14, 28, 30 or 98 tablets in transparent PVC/PVDC/Aluminium blisters.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The easiest way to break the tablet is illustrated below:
- place the tablet with the score on top
- place thumb and index of the same hand on each side of the score line and press as shown on the drawing.

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

7 MARKETING AUTHORISATION HOLDER
Accord Healthcare Limited
319 Pinner Road
North Harrow
Middlesex HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20075/0132

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/09/2008

10 DATE OF REVISION OF THE TEXT
18/09/2008
NAME OF THE MEDICINAL PRODUCT
Lisinopril 20 mg Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains lisinopril dihydrate equivalent to 20 mg anhydrous lisinopril. For full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Tablets. 20 mg tablets are white, round biconvex tablets with embossing “20” on one side and breakline on the other side. The tablets can be divided into equal halves.

CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of hypertension.

Heart Failure
Treatment of symptomatic heart failure.

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

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

4.2 Posology and method of administration
Lisinopril tablets should be administered orally in a single daily dose. As with all other medication taken once daily, Lisinopril tablets should be taken at approximately the same time each day. The absorption of Lisinopril tablets is not affected by food. The dose should be individualised according to patient profile and blood pressure response (see section 4.4)

Hypertension
Lisinopril tablets may be used as monotherapy or in combination with other classes of antihypertensive medicinal products.

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

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

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

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

Table 3 Dosage adjustment in renal impairment.

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Starting Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 10 ml/min (including patients on dialysis)</td>
<td>2.5 mg*</td>
</tr>
<tr>
<td>10-30 ml/min</td>
<td>2.5-5 mg</td>
</tr>
<tr>
<td>31-80 ml/min</td>
<td>5-10 mg</td>
</tr>
</tbody>
</table>

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure
In patients with symptomatic heart failure, Lisinopril tablets should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. Lisinopril tablets may be initiated at a starting dose of 2.5 mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of Lisinopril tablets should be increased:
By increments of no greater than 10 mg
At intervals of no less than 2 weeks
To the highest dose tolerated by the patient up to a maximum of 35 mg once daily.
Dose adjustment should be based on the clinical response of individual patients.
Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Lisinopril tablets. Renal function and serum potassium should be monitored (see section 4.4).

Acute Myocardial Infarction
Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with Lisinopril tablets.
Starting dose (first 3 days after infarction)
Treatment with Lisinopril tablets may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Lisinopril tablets is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4).
In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril tablets dosage should be adjusted according to the patient’s creatinine clearance (see Table 1).
Maintenance dose
The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) Lisinopril tablets should be withdrawn.
Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Lisinopril tablets (see section 4.2).
Renal Complications of Diabetes Mellitus
In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg Lisinopril tablets once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg. In cases of renal impairment (creatinine clearance <80 ml/min), the initial Lisinopril tablets dosage should be adjusted according to the patient’s creatinine clearance (see Table 1).

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

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

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

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

4.4 Special warnings and precautions for use

Symptomatic Hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Lisinopril tablets, 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 tablets. 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 tablets may be necessary.

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

**Aortic and mitral valve stenosis / hypertrophic cardiomyopathy**

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

**Renal Function Impairment**

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

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

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

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

**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 tablets. This may occur at any time during therapy. In such cases, Lisinopril tablets 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 4.3 Contraindications).

**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 or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Lisinopril tablets who develop jaundice or marked elevations of hepatic enzymes should discontinue Lisinopril tablets 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 tablets 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 tablets 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 tablets 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 tablets 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 tablets. 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 tablets is generally not recommended (see section 4.5).

Pregnancy and lactation
Lisinopril should not be used during the first trimester of pregnancy. Lisinopril tablets is contraindicated in the second and third trimesters of pregnancy (see section 4.3). When pregnancy is detected, lisinopril treatment should be discontinued as soon as possible (see section 4.6). Use of lisinopril is not recommended during breast-feeding.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics
When a diuretic is added to the therapy of a patient receiving Lisinopril tablets 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 tablets is added. The possibility of symptomatic hypotension with Lisinopril tablets can be minimised by discontinuing the diuretic prior to initiation of treatment with Lisinopril tablets (see section 4.2 and 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 tablets 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 tablets 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 tablets. 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 tablets may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

4.6 Pregnancy and lactation

Pregnancy
Lisinopril tablets should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester toxicity exposure have not appeared to manifest malformations consistent with human foetotoxicity as described below. Lisinopril tablets is contraindicated during the second and third trimester of pregnancy (see section 4.3). Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia, see also section 5.3). Should exposure to Lisinopril tablets have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended. Infants whose mothers have taken Lisinopril tablets should be closely observed for hypotension, oliguria and hyperkalaemia. Lisinopril tablets, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

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

4.7 Effects on ability to drive and use machines
When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

4.8 Undesirable effects
The following undesirable effects have been observed and reported during treatment with Lisinopril tablets 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.

4.9 Overdose
Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating Lisinopril tablets (e.g., emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril tablets 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.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03
Lisinopril tablets is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.
Whilst the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.
The effect of Lisinopril tablets on mortality and morbidity in heart failure has been studied by comparing a high dose (32.5 mg or 35 mg once daily) with a low dose (2.5 mg or 5 mg once daily). In a study of 3164 patients, with a median follow up period of 46 months for surviving patients, high dose Lisinopril tablets produced a 12% risk reduction in the combined endpoint of all-cause mortality and all-cause hospitalisation (p = 0.002) and an 8% risk reduction in all-cause mortality and cardiovascular hospitalisation (p = 0.036) compared with low dose. Risk reductions for all-cause mortality (8%; p = 0.128) and cardiovascular mortality (10%; p = 0.073) were observed. In a post-hoc analysis, the number of hospitalisations for heart failure was reduced by 24% (p=0.002) in patients treated with high-dose Lisinopril tablets compared with low dose. Symptomatic benefits were similar in patients treated with high and low doses of Lisinopril tablets.
The results of the study showed that the overall adverse event profiles for patients treated with high or low dose Lisinopril tablets were similar in both nature and number. Predictable events resulting from ACE inhibition, such as hypotension or altered renal function, were manageable and rarely led to treatment withdrawal. Cough was less frequent in patients treated with high dose Lisinopril tablets compared with low dose.
In the GISSI-3 trial, which used a 2x2 factorial design to compare the effects of Lisinopril tablets and glyceryl trinitrate given alone or in combination for 6 weeks versus control in 19,394 patients who were administered the treatment within 24 hours of an acute myocardial infarction, Lisinopril tablets produced a statistically significant risk reduction in mortality of 11% versus control (2p=0.03). The risk reduction with glyceryl trinitrate was not significant but the combination of Lisinopril tablets and glyceryl trinitrate produced a significant risk reduction in mortality of 17% versus control (2p=0.02). In the sub-groups of elderly (age > 70 years) and females, pre-defined as patients at high risk of mortality, significant benefit was observed for a combined endpoint of mortality and cardiac function. The combined endpoint for all patients, as well as the high-risk sub-groups, at 6 months also showed significant benefit for those treated with Lisinopril tablets or Lisinopril tablets plus glyceryl trinitrate for 6 weeks, indicating a prevention effect for Lisinopril tablets. As would be expected from any vasodilator treatment, increased incidences of hypotension and renal dysfunction were associated with Lisinopril tablets treatment but these were not associated with a proportional increase in mortality.
In a double-blind, randomised, multicentre trial which compared Lisinopril tablets with a calcium channel blocker in 335 hypertensive Type 2 diabetes mellitus subjects with incipient nephropathy characterised by microalbuminuria, Lisinopril tablets 10 mg to 20 mg administered once daily for 12 months, reduced systolic/diastolic blood pressure by 13/10 mmHg and urinary albumin excretion rate by 40%. When compared with the calcium channel blocker, which produced a similar reduction in blood pressure, those treated with Lisinopril tablets showed a significantly greater reduction in urinary albumin excretion rate, providing evidence that the ACE inhibitory action of Lisinopril tablets reduced microalbuminuria by a direct mechanism on renal tissues in addition to its blood pressure lowering effect. Lisinopril treatment does not affect glycaemic control as shown by a lack of significant effect on levels of glycated haemoglobin (HbA1c).
5.2 Pharmacokinetic properties
Lisinopril is an orally active non-sulphydryl-containing ACE inhibitor.

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

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

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

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

Renal impairment
Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. In mild to moderate renal impairment (creatinine clearance 30-80 ml/min) mean AUC was increased by 13% only, while a 4.5-fold increase in mean AUC was observed in severe renal impairment (creatinine clearance 5-30 ml/min). Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55 ml/min.

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

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

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

6.1 List of excipients
Mannitol
Calcium hydrogen phosphate dihydrate
Maize starch
Starch, pregelatinised
Magnesium stearate
Silica, colloidal anhydrous

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Carton containing 14, 28, 30 or 98 tablets in transparent PVC/PVDC/Aluminium blisters.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The easiest way to break the tablet is illustrated below:
- place the tablet with the score on top
- place thumb and index of the same hand on each side of the score line and press as shown on the drawing.

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

7 MARKETING AUTHORISATION HOLDER
Accord Healthcare Limited
319 Pinner Road
North Harrow
Middlesex HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20075/0133

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/09/2008

10 DATE OF REVISION OF THE TEXT
18/09/2008
Lisinopril 5 mg, 10mg & 20mg Tablets
Lisinopril dihydrate

Read all of this leaflet carefully before you start using 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 tablets are and what they are used for
2. Before you use Lisinopril tablets
3. How to use Lisinopril tablets
4. Possible side effects
5. How to store Lisinopril tablets
6. Further information

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

Lisinopril tablets belong to a group of medicines called ACE inhibitors. ACE is short for Angiotensin-Converting Enzyme. ACE inhibitors cause the body to produce less angiotensin (a hormone which tightens blood vessels and increases blood pressure), resulting in a reduction in pressure inside blood vessels and an improvement in heart function.

Lisinopril tablets are used:
1. in the treatment of high blood pressure (hypertension).
2. in patients whose heart is unable to pump properly (heart failure).
3. after an acute heart attack.
4. to treat kidney problems due to diabetes in hypertensive patients.

2. BEFORE YOU USE LISINOPRIL TABLETS

Do not use Lisinopril tablets:
- if you are allergic (hypersensitive) to lisinopril or any of the other ingredients of Lisinopril tablets (see section 6. "Further Information") or to any other angiotensin converting enzyme (ACE) inhibitor.
- if you have ever had an allergic reaction during previous treatment with ACE inhibitors. Symptoms of an allergic reaction are: a sudden build-up of fluid in the skin and mucous membranes (e.g. throat or tongue), breathing difficulties and/or itching and skin rash (angioedema). Similarly, do not take Lisinopril tablets if someone in your family has had a similar reaction.
- if you have ever had an angioedema of unknown cause.
- if you are pregnant during the 2nd or 3rd trimester. For use during the first trimester, see section "Pregnancy and breast-feeding".
- if you are breast-feeding or wish to breastfeed.

Take special care with Lisinopril tablets:
- if you are prone to fainting and suffer from dizziness (occasional low blood pressure). The risk of low blood pressure is greater if you are using a diuretic (water pill), if you are on a low-salt diet, if you receive dialysis, or if you have vomiting or diarrhoea.
- if you have a narrowing of the aorta, renal artery or mitral valve in the heart, or thickening of the heart muscle.
- if you have kidney problems.
- if you have a dark skin colour, as Lisinopril tablets may be less effective in people with a dark skin colour.
- if you experience a persistent dry cough.
- if you are at greater risk of too much potassium in the blood as a result of reduced kidney function, diabetes or using potassium-sparing medicines such as spironolactone or medicines containing potassium. Having too much potassium in the blood can cause symptoms such as muscle cramps, diarrhoea, nausea, dizziness and headache.
- if you are to undergo an operation or an anaesthetic.
- if you have diabetes.
- if you are breast-feeding or wish to breastfeed.

Please consult your doctor if any of the above-mentioned situations applies to you, or has ever applied to you in the past.

Using 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, this applies to:

- **medicines containing potassium.** Taking these at the same time as Lisinopril tablets may lead to excessive levels of potassium in the blood.
- **diuretics (water pills) including potassium-sparing diuretics such as spironolactone, triamterene or amiloride** (used to treat high blood pressure). If taken at the same time as Lisinopril tablets, the blood pressure-lowering effect may be enhanced.
- **lithium** (a drug used to treat manic depression). If taken at the same time as Lisinopril tablets, the amount of lithium may increase in the blood.
- **painkillers with an anti-inflammatory and fever-reducing effect (NSAIDs), and if you take more than 3 grams of aspirin a day.** If taken at the same time, the blood pressure-lowering effect of Lisinopril tablets may be reduced.
- **other medicines to treat high blood pressure (antihypertensives).** If taken at the same time, the blood pressure-lowering effect of Lisinopril tablets may be enhanced.
- **medicines used to treat depression** (tricyclic antidepressants), **psychosis** (antipsychotics) and **narcotics (anaesthetics).** If taken at the same time, the blood pressure-lowering effect of Lisinopril tablets may be reduced further.
- **medicines that have a stimulating effect on a certain part of the central nervous system** (sympathomimetics). If taken at the same time, the blood pressure-lowering effect of Lisinopril tablets may be reduced.
- **medicines that suppress your immune system.**
- **alloplurinol, a medicine used in the treatment for gout.**
- **medicines used in the treatment of diabetes** (antidiabetics). If taken at the same time, the blood glucose-lowering effect of antidiabetics may be enhanced.

Lisinopril can be used at the same time as aspirin (at low doses), **blood-thinners** (thrombolytic agents), medicines used in high blood pressure (beta-blockers) and/or medicines used to treat a painful, tight sensation in the chest (angina pectoris) (nitrates).

**Pregnancy and breast-feeding**

Please consult your doctor if you are pregnant or wish to become pregnant. Lisinopril tablets **may not be used during pregnancy in the second trimester.** There is not enough information available on the safety of Lisinopril tablets during the first three months of pregnancy. Lisinopril tablets are therefore not recommended to be used during the first trimester of pregnancy. In the second and third trimesters, Lisinopril tablets may harm your unborn child.

It is not known whether Lisinopril tablets pass into breast milk. **Do not use Lisinopril tablets if you are breastfeeding.**

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

**Driving and using machines**

Lisinopril tablets may cause dizziness and tiredness. If you should experience dizziness or tiredness, do not drive any vehicles and/or use machinery that requires alertness.

### 3 HOW TO USE LISINOPRIL TABLETS

Always use Lisinopril tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Usual dosages are as follows:

1. **High blood pressure (hypertension)**
   Lisinopril tablets can be used alone or in combination with other medicines that lower blood pressure.
   **Starting dose:** take 10 mg of Lisinopril tablets once a day.
   **Maintenance dose:** take 20 mg of Lisinopril tablets once a day.
   * Patients on diuretics (water pills): consult your doctor before you start using Lisinopril tablets.
   * Patients with reduced kidney function: consult your doctor. Your dosage will probably have to be adjusted.

2. **Patients whose heart is unable to pump properly (heart failure)**
   Lisinopril tablets are generally used alongside treatment with diuretics (water pills), digitalis or beta-blockers.
   **Starting dose:** take 2.5 mg of Lisinopril tablets once a day (one half Lisinopril tablets 5 mg tablet).
   Dosage will be adjusted depending on how your body responds to treatment.

3. **After an acute heart attack**
   Lisinopril tablets treatment should begin within 24 hours after onset of heart attack.
   **Starting dose** (for the first 3 days **after the heart attack**): 5 mg Lisinopril tablets, followed by another 5 mg Lisinopril tablets 24 hours later, followed by 10 mg Lisinopril tablets after a further 24 hours and then 10 mg Lisinopril tablets once a day. Your dose will be adjusted if you suffer from low blood pressure or impaired kidney function.
   **Maintenance dose:** take 10 mg Lisinopril tablets once a day. If your blood pressure drops too low, your dosage will be lowered or discontinued. After 6 weeks, you will be checked to see whether you can stop taking Lisinopril tablets or whether treatment must be continued.

4. **Kidney problems due to diabetes (Type 2 diabetes mellitus) in hypertensive patients**
   **(Starting) dose:** take 10 mg Lisinopril tablets once a day. If necessary, your dose can be increased to 20 mg Lisinopril tablets once a day.
   * Patients with reduced kidney function: consult your doctor. Your dosage will probably have to be adjusted.

**Children**

Use of Lisinopril tablets in children is not advised, as its safety and effectiveness have not been fully established.

**Elderly**

In the elderly, Lisinopril tablets can be used as above. However, it must be remembered that kidney function may be impaired in the elderly.
Kidney transplant patients
Use of Lisinopril tablets in kidney transplant patients is not recommended, as there is no experience in this patient group.

Directions for use
Take Lisinopril tablets every day at around the same time. Choose a time that is easy to remember; before a meal, for example.

The easiest way to break the tablet is illustrated below:
place the tablet so that the break line is facing towards you;
then, using your index finger and thumb of the same hand, press downwards and outwards on either side of the break line, as shown in the diagram.

If you have the impression that Lisinopril tablets have an effect which is too strong or too weak, talk to your doctor or pharmacist.

If you use more Lisinopril tablets than you should:

Symptoms
There are limited data available on the effect of taking very high doses. Symptoms that might occur include low blood pressure, circulatory arrest, sodium (salt) imbalance, kidney dysfunction, hyperventilation, rapid and slow heartbeat, heart palpitations, dizziness, anxiety and coughing.

What you must do:
If you have used or taken too much Lisinopril tablets, please contact your doctor or pharmacist immediately. Try to find out how much Lisinopril tablets have been taken. Keep the Lisinopril tablets carton close at hand.

If you forgot to take Lisinopril tablets:
You can still take Lisinopril tablets for up to 12 hours after the usual time. If more than 12 hours have passed, skip the forgotten dose and take your next tablet at the usual time. Do not take a double dose of Lisinopril tablets to make up for a forgotten dose.

If you stop using Lisinopril tablets:
There is a risk that the symptoms - for which Lisinopril tablets had originally been prescribed - will return.

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 tablets can cause side effects, although not everybody gets them.

Rarely patients may experience a sudden build-up of fluid in the skin and mucous membranes (e.g. throat or tongue), breathing difficulties and/or itching and skin rash, often as an allergic reaction (angioedema). If this happens, you should stop taking this treatment and see your doctor.
Very rarely patients may experience liver problems, with jaundice. If this happens you should stop taking this treatment and see your doctor.
Very rarely patient may develop a certain serious blood disorder (a lack of white blood cells) accompanied by an increased susceptibility to infections (neutropenia) or by sudden high fever, severe sore throat and mouth ulcers (agranulocytosis). Contact your doctor immediately if you develop such symptoms.

Side effects are:
• very common (occurring in more than one in 10 patients);
• common (occurring in more than one in 100, but less than one in 10 patients);
• uncommon (occurring in more than one in 1,000, but less than one in 100 patients);
• rare (occurring in more than one in 10,000, but less than one in 1,000 patients);
• very rare, including isolated reports (occurring less than one in 10,000 patients).

Effects on the blood and lymphatic system
very rare: blood disorders (e.g. a drop in blood haemoglobin levels, reduction in haematocrit).
very rare: blood and lymphatic system disorders accompanied by an increased susceptibility to infections, anaemia, haemolytic anaemia.

Effects on the metabolism
very rare: excessively low blood sugar levels, accompanied by feelings of hunger, sweating, dizziness and heart palpitations (hypoglycaemia).

Effects on the nervous system and psychiatric disorders
common: dizziness and headache.
uncommon: mood swings, pins and needles/itching without apparent cause, dizziness, taste disorders, sleep disorders.

rare: mental confusion.
Effects on the heart and blood vessels
common: drop in blood pressure caused by getting up too quickly from a sitting or lying position for example, sometimes accompanied by dizziness.
uncommon: heart attack or stroke, heart palpitations, increased heartbeat, paleness of the fingers or toes (Raynaud's phenomenon).

Effects on the respiratory system
common: coughing.
uncommon: inflammation of the nose lining, characterised by a blocked or runny nose and sneezing (rhinitis).
very rare: tight-chestedness caused by muscle spasms in the airways, inflammation of the paranasal sinuses (sinusitis), pneumonia.

Effects on the gastrointestinal tract (stomach and intestine)
common: diarrhoea and vomiting.
uncommon: nausea, abdominal pain and impaired digestion.
rare: dry mouth.
very rare: inflammation of the pancreas accompanied by severe upper abdominal pain radiating to the back, as well as nausea and vomiting, fluid build-up in the intestinal wall (recognisable by such symptoms as abdominal pain), inflammation of the liver (hepatitis) accompanied by jaundice (yellow discolouration of the skin).

Effects on the skin
uncommon: skin rash and itching.
rare: hypersensitivity (allergy), sudden build-up of fluid in the face, tongue, limbs, breathing difficulties and/or itching and skin rash (angioedema), skin rash with severe itching and wheal formation (urticaria or hives), loss of hair, recurring skin disease with peeling dry skin rash (psoriasis).
very rare: excessive sweating, formation of blister clusters over the skin, severe, sudden (hypersensitive) reaction with fever and blisters/peeling of the skin, severe hypersensitive reaction with (high) fever, red spots on skin, painful joints and/or eye inflammation, skin rash with red (weeping) irregular-shaped spots.

Combinations of the following side effects have also been reported: inflamed blood vessels, muscle pain, painful joints, inflamed joints, certain blood disorders, hypersensitivity to sunlight and other skin reactions.

Effects on the kidneys and urinary tract
common: reduced kidney function.
rare: poor kidney function, acute kidney problems.
very rare: reduced or no urine output.

Effects on the reproductive system and breasts
uncommon: impotence.
rare: male breast formation.

General effects
uncommon: tiredness and weakness.

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 TABLETS
Keep out of the reach and sight of children.
Do not store above 30°C
Do not use Lisinopril tablets after the expiry date which is stated on the carton after “do not use after” or “exp”. The expiry date refers to the last day of that month.

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

6. FURTHER INFORMATION
What Lisinopril tablets contain
- The active substance is lisinopril dihydrate. Each Lisinopril tablets 5 mg, 10 mg and 20 mg tablet contains lisinopril dihydrate, equivalent to 5, 10 and 20 mg of lisinopril, respectively.
- The other ingredients are mannitol, calcium hydrogen phosphate dihydrate, maize starch, pregelatinised starch, magnesium stearate and colloidal anhydrous silica.

What Lisinopril tablets looks like and contents of the pack
- 5 mg tablets are white, round biconvex tablets with embossing “5” on one side and breakline on the other side.
- 10 mg tablets are white, round biconvex tablets with embossing “10” on one side and breakline on the other side.
- 20 mg tablets are white, round biconvex tablets with embossing “20” on one side and breakline on the other side.

Packed in boxes containing strips of 14, 28, 30 or 98 tablets.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
For any information about this medicinal product, please contact the Marketing Authorisation Holder: Accord Healthcare Limited, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, UK.

Manufacturer
PSI nv, Kraanlei 27, 9000 Ghent, Belgium.

This leaflet was last approved in July 2006