**Lisinopril 2.5 mg Tablets**
**Lisinopril 5 mg Tablets**
**Lisinopril 10 mg Tablets**
**Lisinopril 20 mg Tablets**

PL 17907/0236-9

**UKPAR**

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Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets

PL 17907/0236-9

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 17907/0236-9) on 16 February 2012. These are prescription-only medicines (POM).

Lisinopril belongs to a group of medicines called angiotensin-converting enzyme (ACE) inhibitors that work by widening blood vessels, making it easier for the heart to pump blood through them. This helps to lower blood pressure and can also help the heart to work better if it does not pump as well as required.

Lisinopril can be used for the following:

- To treat high blood pressure (hypertension)
- To treat heart failure
- If you have recently had a heart attack (myocardial infarction)
- To treat kidney problems caused by Type II diabetes in people with high blood pressure

Lisinopril is recommended in children (above 6 years old) only for the treatment of high blood pressure. Lisinopril should not be used in children with severe kidney impairment.

These Marketing Authorisations for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets are considered to be identical to the previously granted licences for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 17907/0020-23), authorised to Bristol Laboratories Limited on 25 November 2003.

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

PL 17907/0236-9

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bristol Laboratories Limited Marketing Authorisations for the medicinal products Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 17907/0236-9) on 16 February 2012. The products are prescription-only medicines.

These are simple, abridged, ‘informed consent’ applications, submitted according to Article 10(c) of EC Directive 2001/83 (as amended), cross-referencing the Marketing Authorisations for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 17907/0020-23), authorised to Bristol Laboratories Limited on 25 November 2003.

Lisinopril Tablets are indicated for the following:

- **Hypertension**: For the treatment of all grades of essential hypertension and renovascular hypertension. Lisinopril may be used alone or in conjunction with other anti-hypertensive agents. There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications (see section 5.1 of SmPC). Lisinopril is not recommended in children in other indications than hypertension.

- **Congestive heart failure**: As adjunctive therapy with non-potassium sparing diuretics and, where appropriate, digitalis. Treatment should be initiated under close medical supervision (in hospital for severe heart failure).

- **Acute myocardial infarction**: For the treatment of haemodynamically stable patients within 24 hours of acute myocardial infarction, to prevent development of left ventricular dysfunction or heart failure and to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blocker.

- **Diabetic nephropathy**: In normotensive insulin dependent and hypertensive non-insulin dependent diabetes mellitus patients who have incipient nephropathy characterised by microalbuminuria, lisinopril reduces urinary albumin excretion rate.

Lisinopril inhibits the angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

While 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.

ACE is known to be present in the endothelium and increased ACE activity in
diabetic patients, which results in the formation of Angiotensin II and destruction of
bradykinin, potentiates the damage to the endothelium caused by hyperglycaemia.
ACE inhibitors, including lisinopril, inhibit the formation of angiotensin II and
breakdown of bradykinin and hence ameliorate endothelial dysfunction.

The effect of lisinopril on urinary albumin excretion rate in diabetic patients is
mediated by a reduction in blood pressure as well as a direct mechanism on the renal
tissue.

As the applications are for products that are identical to already authorised reference
products, for which safety concerns requiring additional risk minimisation have not
been identified, a risk minimisation system is not considered necessary. The reference
products have been in use for many years and the safety profile of the active is well-
established.

It is not considered that these medicinal products represent any risk to the
environment. There is no reason to conclude that marketing of these products will
change the overall use pattern of the existing market. The availability of these
medicinal products, which are identical to the cited reference products, will not lead to
any increase in environmental exposure concentrations of the active ingredient. An
Environmental Risk Assessment (ERA) is not considered necessary.

The MHRA considers that the pharmacovigilance system described by the Marketing
Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence
that the MAH has the services of a Qualified Person (QP) responsible for
pharmacovigilance and has the necessary means for the notification of any adverse
reaction suspected of occurring either in the Community or in a third country.

No new data were submitted nor was it necessary for these simple applications, as the
data are identical to those of the previously granted cross-reference products. As the
cross-reference products were first granted prior to the introduction of current
legislation, no Public Assessment Report (PAR) was generated for them.
PHARMACEUTICAL ASSESSMENT

LICENCE NUMBERS: PL 17907/0236-9

PROPRIETARY NAME: Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets

ACTIVE INGREDIENTS: Lisinopril

COMPANY NAME: Bristol Laboratories Limited

E.C. ARTICLE: Article 10(c) of Directive 2001/83/EC (as amended)

LEGAL STATUS: POM

1. INTRODUCTION

These are simple abridged applications, submitted under Article 10(c) of Directive 2001/83/EC (as amended) for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets. The proposed MAH is Bristol Laboratories Limited.

The reference products are Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 17907/0020-23), authorised to Bristol Laboratories Limited on 25 November 2003. The proposed and reference products are identical.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The approved names of the products are Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets. The products have been named in line with current requirements and the product names are acceptable.

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

Each tablet contains 2.5 mg, 5 mg, 10 mg or 20 mg of the active ingredient lisinopril. The tablets are licensed for marketing in the following packaging:

- Polyvinyl chloride (PVC) / aluminium foil blister strips - pack sizes of 28, 56 or 84 tablets
- High Density Polyethylene (HDPE) tablet containers - pack sizes of 30, 60, 250 or 500 tablets

The blister strips and HDPE containers are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The MAH has stated that not all pack sizes may be marketed. The container closure systems and pack sizes are consistent with those for the reference products.

The approved shelf-life (3 years) and storage conditions (‘Do not store above 25°C. Store in the original package’ for the blister packs; ‘Do not store above 25°C. Keep the container tightly closed’ for the HDPE container packs) are consistent with the details registered and data submitted for the reference products.
2.3 Legal status
POM - The products are available subject to a medical prescription.

2.4 Marketing Authorisation Holder / Contact Persons/Company
The proposed Marketing Authorisation Holder is ‘Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts HP4 1EG’.

The Qualified Person (QP) responsible for pharmacovigilance was stated and their CV included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance 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 sizes are stated.

2.8 Finished product / shelf-life specification
The proposed finished product specifications are in line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
The magnesium stearate and calcium hydrogen phosphate have been confirmed as being of vegetable origin. There are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms.

3. EXPERT REPORT
A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The 2.5 mg strength tablets are white to almost white, circular, biconvex, uncoated tablets with ‘2.5’ embossed on one side and ‘BL’ embossed on the other side. The 5 mg strength tablets are light pink coloured, circular, biconvex, uncoated tablets with a breakline and ‘5’ embossed on one side and ‘BL’ embossed on the other side. The 10 mg strength tablets are light
pink coloured, circular, biconvex, uncoated tablets with ‘10’ embossed on one side and ‘BL’ embossed on the other side. The 20 mg strength tablets are pink coloured, circular, biconvex, uncoated tablets with ‘20’ embossed on one side and ‘BL’ embossed on the other side. The appearances of the products are consistent with those of the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The approved SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL) / LABELLING

PIL

The approved PIL is satisfactory and in line with the approved SmPCs. It has been prepared according to the Quality Review of Documents (QRD) template and is consistent with the details registered for the cross-reference products. A mock-up PIL has been provided. The PIL user-testing report has been evaluated and is accepted. It supports the readability of the package leaflet.

Labelling

Mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for currently unmarketed pack sizes to the MHRA for approval before those packs are commercially marketed.

7. CONCLUSIONS

The grounds for these applications are considered adequate. Marketing Authorisations were therefore granted.
NON-CLINICAL ASSESSMENT

These are simple, abridged, ‘informed consent’ applications made under Article 10(c) of EC Directive 2001/83 (as amended).

No new non-clinical data have been supplied with these applications and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.
CLINICAL ASSESSMENT

These are simple, abridged, ‘informed consent’ applications made under Article 10(c) of EC Directive 2001/83 (as amended), cross-referring to the Marketing Authorisations for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 17907/0020-23; Bristol Laboratories Limited).

No new clinical data have been supplied with the applications, and none are required for applications of this type. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are considered identical to the previously granted licences for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 17907/0020-23; Bristol Laboratories Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs, PIL and labelling are satisfactory and consistent with the details registered for the cross-reference products.

A mock-up PIL has been provided. The package leaflet is in line with the SmPCs and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the MHRA for approval before those packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. The benefit: risk ratio is considered to be positive.
Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets

PL 17907/0236-9

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation applications on 07 July 2006.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 15 August 2006.

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 02 October 2006, 21 January 2008 and 18 April 2011.

4 The applicant responded to the MHRA’s requests, providing further information for the quality sections on 28 March 2007, 05 September 2008 and 07 December 2011 respectively.

5 The applications were determined on 16 February 2012.
Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets

PL 17907/0236-9

 STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 17907/0236-9) is as follows – Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT
Lisinopril 2.5 mg Tablets
Lisinopril 5 mg Tablets
Lisinopril 10 mg Tablets
Lisinopril 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Lisinopril 2.5/5/10/20 mg (as dihydrate)
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
White to almost white, circular, biconvex, uncoated tablets with ‘2.5’ embossing on one side & ‘BL’ embossing on the other side.
Light pink coloured, circular, biconvex, uncoated tablets with ‘5’ embossing and breakline on one side and ‘BL’ embossing on the other side.
Light pink coloured, circular, biconvex, uncoated tablets with ‘10’ embossing on one side and ‘BL’ embossing on the other side.
Pink coloured, circular, biconvex, uncoated tablets with ‘20’ embossing on one side and ‘BL’ embossing on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension: For the treatment of all grades of essential hypertension and renovascular hypertension. May be used alone or in conjunction with other anti-hypertensive agents.

Congestive heart failure: As adjunctive therapy with non-potassium sparing diuretics and where appropriate digitalis. Treatment should be initiated under close medical supervision (in hospital for severe heart failure).

Acute myocardial infarction: For the treatment of haemodynamically stable patients within 24 hours of acute myocardial infarction, to prevent development of left ventricular dysfunction or heart failure and to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blocker.

Diabetic nephropathy: In normotensive insulin dependent and hypertensive non-insulin dependent diabetes mellitus patients who have incipient nephropathy characterised by microalbuminuria, lisinopril reduces urinary albumin excretion rate.

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

The dose should be individualised according to patient profile and blood pressure response (see section 4.4).
**Hypertension**
Lisinopril may be used as monotherapy or in combination with other classes of antihypertensive therapy.

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

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

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

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

**Table 1 Dosage adjustment in renal impairment**

<table>
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<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>
</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.

**Use in hypertensive paediatric patients aged 6–16 years**
The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients ≥50 kg. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in paediatric patients (see section 5.1).

In children with decreased renal function, a lower starting dose or increased dosing interval should be considered.
**Heart failure**

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

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

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

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

**Acute myocardial infarction**

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

**Starting dose (first 3 days after infarction)**

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

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

**Maintenance dose**

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

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

**Renal complications of diabetes mellitus**

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

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

**Paediatric use**

There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications (see section 5.1). Lisinopril is not recommended in children in other indications than hypertension.

Lisinopril is not recommended in children below the age of 6, or in children with severe renal impairment (GFR <30 ml/min/1.73 m²) (see section 5.2).
Use in the elderly
In clinical studies, there was no age-related change in the efficacy or safety profile of the drug. When advanced age is associated with decrease in renal function, however, the guidelines set out in Table 1 should be used to determine the starting dose of Lisinopril. Thereafter, the dosage should be adjusted according to the blood pressure response.

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

4.3 Contraindications
- Hypersensitivity to lisinopril, any other ACE inhibitor or any of the other ingredients.
- History of angioneurotic oedema related to previous treatment with an ACE inhibitor.
- Hereditary or idiopathic angioedema.
- Chronic severe renal failure (creatinine clearance of <30ml/min).
- Bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.
- Cardiogenic shock.
- Acute myocardial infarction with haemodynamic instability.
- Pregnancy.
- Lactation.

4.4 Special warnings and precautions for use

Assessment of renal function
Renal function should be assessed and salt and or fluid deficiency corrected prior to initiation of therapy. During therapy, regular checks of blood pressure and renal function particularly in “at risk” patients is necessary.

“At risk” patients include the elderly; patients with severe heart failure; renal impairment; dehydration; severe renal arterial hypertension; connective tissue disease; impaired immune response; or patients who are receiving concurrent treatment with immunosuppressants including steroids, antimetabolites or cytotoxic drugs.

Impaired renal function
Lisinopril should be used with caution in patients with evidence of renal insufficiency, as they may require reduced or less frequent doses. Close monitoring of renal function during therapy should be performed in these patients. Any renal impairment induced by lisinopril is usually reversible if diagnosed and treated promptly.

Renal failure has been reported in association with ACE inhibitors, mainly in patients with severe congestive heart failure or underlying renal disease.

Haemodialysis patients
Sudden and potentially life threatening anaphylactoid reactions have been reported in some patients dialysed with high–flux membranes (e.g. AN69) and treated concomitantly with an ACE inhibitor. This combination should therefore be avoided.

In acute myocardial infarction
Lisinopril treatment should not be initiated in patients with evidence of renal dysfunction (serum creatine concentration >177micromol/l and/or proteinuria >500 mg/24h). The physician should consider withdrawing lisinopril therapy if renal dysfunction develops during treatment (serum creatinine concentration >265 micromol /l or a doubling of pre-treatment value).
Symptomatic hypotension
Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. This is more likely to occur in those who have been volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting. The possibility of this occurring is reduced by discontinuing diuretic therapy or significantly reducing the diuretic dose 2 to 3 days before starting lisinopril treatment.

Severe hypotension has been reported with ACE inhibitors, mainly in those with severe heart failure. In patients at risk, lisinopril treatment and its’ dose adjustment should be monitored under close medical supervision. If hypotension develops the patient should be placed in a supine position. Volume repletion with oral fluids or intravenous normal saline may be required. If there is associated bradycardia, intravenous atropine may be required. Lisinopril treatment may be restarted with careful dose titration once effective blood volume and pressure is restored. Similar caution and close supervision may also apply to patients with ischaemic heart or cerebrovascular disease, in whom severe hypotension could result in a myocardial infarct or cerebrovascular accident.

Lisinopril should be given with caution to patients with aortic stenosis or hypertrophic cardiomyopathy.

In some patients with congestive heart failure with normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. A reduction of dose or discontinuation of lisinopril may be necessary if such hypotension becomes symptomatic.

The appearance of hypotension after the initial dose of lisinopril does not preclude subsequent careful dose adjustment with the drug after effective management of hypotension.

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

Angioedema/anaphylactoid reactions (see 4.3 Contraindications)
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including lisinopril. This may occur at any time during treatment. Lisinopril should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. Emergency therapy should be administered promptly if the tongue, glottis or larynx are involved as this is likely to cause airways obstruction; adrenaline should be administered and/or maintenance of the airways.

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

LDL-apheresis/desensitisation therapy: Patients receiving ACE inhibitors during LDL-apheresis with dextran-sulphate columns or desensitisation treatment (eg. hymenoptera venom) have sustained anaphylactoid reactions.

Race
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. When lisinopril is used as a single agent in hypertension, Afro-Caribbean patients may show a reduced therapeutic response.

Cough
A non-productive, persistent cough has been reported with the use of ACE inhibitors, almost always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.
Use in Hypertensive Paediatric Patients aged 6-16 years
The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once
daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 20 mg
daily in patients weighing 20 to <50 kg, and 40 mg in patients ≥50 kg. Doses above 0.61
mg/kg (or in excess of 40 mg) have not been studied in paediatric patients (see section 5.1).

In children with decreased renal function, a lower starting dose or increased dosing interval
should be considered.

Paediatric Use:
There is limited efficacy and safety experience in hypertensive children >6 years old, but no
experience in other indications (see section 5.1). Lisinopril is not recommended in children in
other indications than hypertension.

Lisinopril is not recommended in children below the age of 6, or in children with severe renal
impairment (GFR <30ml/min/1.73m²) (see section 5.2).

Hyperkalaemia
Hyperkalaemia may occur during treatment with ACE inhibitors, especially in the presence of
renal insufficiency and/or heart failure. Potassium supplements or potassium sparing diuretics
are generally not recommended, since they may lead to significant increases in plasma
potassium. If concomitant use of the above mentioned agents is deemed appropriate, they
should be used with frequent monitoring of serum potassium.

Surgery/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce
hypotension, lisinopril blocks 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.

Aortic stenosis/hypertrophic cardiomyopathy
Lisinopril should not be used in patients with aortic stenosis, cor pulmonale or left ventricular
outflow tract obstruction.

Neutropenia/agranulocytosis
The risk of neutropenia appears to be dose- and type-related and is dependent on the patient’s
clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some
degree of renal impairment especially when it is associated with collagen vascular disease e.g.
 systemic lupus erythematosus, scleroderma and therapy with immunosuppressive agents. It is
 reversible after discontinuation of ACE inhibitor.

Primary hyperaldosteronism: Patients with this disorder may experience a poor response to
lisinopril.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended combinations
Potassium sparing diuretics or potassium supplements: Use of lisinopril with potassium-
sparing diuretics, potassium supplements, or potassium-containing salt substitutes is not
recommended as may lead to significant increases in serum potassium. Lisinopril may elevate
plasma potassium in patients with renal failure.

Precautions for use
Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with
drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was
usually reversible upon discontinuation of lithium and the ACE inhibitor. It is recommended
that serum lithium levels be monitored frequently if lisinopril is administered concomitantly
with lithium.
**Anaesthetic medicinal products:** Use of lisinopril with anaesthetic agents may cause hypotension.

**Antihypertensive agents:** Hypotension may occur when used concurrently with other antihypertensive agents such as beta-blockers, diuretics or vasodilators e.g. calcium channel blockers, moxonidine etc.

**Allopurinol, cytotoxic and immunosuppressive agents:** all increase the risk of leucopenia when given concomitantly with lisinopril.

**Insulin or oral hypoglycaemics:** diabetic patients receiving insulin or oral hypoglycaemics, treated with ACE inhibitors are at increased risk of developing hypoglycaemia.

**Take into account**

**Non-steroidal Anti-inflammatory medicinal products:** Indometacin may reduce the antihypertensive efficacy of lisinopril. In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs (NSAID’s), the co-administration of lisinopril may result in a further deterioration in renal function.

**Alcohol:** potentiation of hypotensive effect with alcohol consumption.

### 4.6 Pregnancy and lactation

Lisinopril is contraindicated in pregnancy and should be stopped if pregnancy is suspected. ACE inhibitors can cause foetal and neonatal morbidity and death when administered to pregnant women during the second and third trimester.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with foetal and neonatal injury, including hypotension, hyperkalaemia and/or skull hypoplasia in the newborn, renal failure, and death. Maternal oligohydramnios has also been reported, presumably resulting from decreased foetal renal function; and may result in foetal limb contractures, craniofacial deformation, and hypoplastic lung development. These adverse events do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalaemia. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

**Use during lactation**

Contraindicated in breast feeding mothers as it is not known whether lisinopril is excreted in human milk.

### 4.7 Effects on ability to drive and use machines

None to negligible influence. Lisinopril may slow individual reactions because of hypotension/dizziness and may impair ability to drive or operate machinery. This effect is enhanced in the presence of alcohol. Patients should be advised not to drive or operate machinery if affected.

### 4.8 Undesirable effects

The most common reported adverse effects with ACE inhibitors include hypotension, headache, dizziness, diarrhoea, fatigue, nausea, persistent dry cough, skin rashes, asthenia.

Other more rare adverse effects reported are:

**Blood and the lymphatic system disorders:** hyperkalaemia and hyponatraemia have occurred. Bone marrow depression manifest as anaemia, and/or thrombocytopenia and/or leucopenia; agranulocytosis; small decreases in haemoglobin and haematocrit (rarely of
clinical significance). There have been reports of haemolytic anaemia although no causal relationship has been established.

**Nervous system disorders:** mood changes, confusion, vertigo, paraesthesia, taste and sleep disturbances.

**Cardiac disorders:** myocardial infarction or cerebrovascular accident (possibly secondary to excessive hypotension in high risk patients), palpitations, tachycardia.

**Respiratory disorders:** bronchospasm, rhinitis, sinusitis.

**Gastrointestinal disorders:** abdominal pain, indigestion, vomiting, dry mouth, hepatitis, jaundice, pancreatitis.

**Skin and subcutaneous disorders:** diaphoresis, alopecia, pruritus, urticaria, psoriasis and severe skin disorders including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme. Angioneurotic oedema of the face, extremeties, lips, tongue, glottis and/or larynx (see 4.4)

**Renal and urinary disorders:** acute renal failure, renal dysfunction (see 4.4), impotence, oliguria/anuria, uraemia.

**General disorders:** a symptom complex has been reported which may include one or more of the following: fever, vasculitis, arthralgia, arthritis, myalgia, positive ANA, elevated ESR, eosinophilia and leucocytosis, rash, photosensitivity or other skin conditions.

**Laboratory test findings:** increases in blood urea, serum creatinine, liver enzymes and serum bilirubin have been seen.

### 4.9 Overdose

The symptoms of overdosage may include severe hypotension, electrolyte disturbance especially hyperkalaemia and renal failure. The patient should be kept under very close supervision and measures employed to prevent absorption and to speed elimination. If severe hypotension occurs, the patient should be placed in the shock position and an intravenous infusion of normal saline solution should be given. Treatment with angiotensin II (if available) may be considered. ACE inhibitors may be removed from the circulation by haemodialysis. The use of high flux dialysis membranes should be avoided. Serum electrolytes and creatinine should be monitored frequently.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

ATC code: CO9A, A03 – Agents Acting on the Renin-Angiotensin System, ACE Inhibitors, plain

Lisinopril inhibits the angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

While 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.

ACE is known to be present in the endothelium and increased ACE activity in diabetic patients, which results in the formation of Angiotensin II and destruction of bradykinin, potentiates the damage to the endothelium caused by hyperglycaemia. ACE inhibitors, including lisinopril, inhibit the formation of angiotensin II and breakdown of bradykinin and hence ameliorate endothelial dysfunction.

The effect of lisinopril on urinary albumin excretion rate in diabetic patients is mediated by a reduction in blood pressure as well as a direct mechanism on the renal tissue.

5.2 Pharmacokinetic properties

Following oral administration of lisinopril, peak serum concentrations of lisinopril 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. 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.

Lisinopril does not appear to be bound to other serum proteins. Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with large intersubject variability (6-60%) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract. The absolute bioavailability of lisinopril is reduced to 16% in patients with stable NYHA Class II-IV congestive heart failure, and the volume of distribution appears to be slightly smaller than that in normal subjects. The oral bioavailability of lisinopril in patients with acute myocardial infarction is similar to that in healthy volunteers.

Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours. Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. Above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and area under the plasma concentration time curve (AUC) than younger patients. Lisinopril can be removed by haemodialysis.

5.3 Preclinical safety data

No data of relevance to the prescriber, which is additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

For a full list of excipients

Calcium Hydrogen Phosphate
Mannitol (E421)
Maize Starch
Magnesium Stearate
Ferrie Oxide E172 (for 5 mg, 10 mg and 20 mg strengths only)

6.2 Incompatibilities

A high incidence of anaphylactoid reactions has been reported in some patients dialysed with high-flux membranes (e.g. AN69) and treated concomitantly with an ACE inhibitor. This combination should therefore be avoided.
6.3 Shelf life
3 years

6.4 Special precautions for storage
Blisters : Do not store above 25°C. Store in the original package.
Containers: Do not store above 25°C. Keep the container tightly closed.

6.5 Nature and contents of container
HDPE tablet containers, pack sizes of 30, 60, 250 or 500 tablets
Al / PVC blister, pack sizes of 28, 56 or 84 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road
Berkhamsted
Hertfordshire, HP4 1EG
United Kingdom

8 MARKETING AUTHORITY NUMBER(S)
PL 17907 / 0236
PL 17907 / 0237
PL 17907 / 0238
PL 17907 / 0239

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
16/02/2012

10 DATE OF REVISION OF THE TEXT
16/02/2012
UKPAR Lisinopril 2.5, 5, 10 and 20 mg Tablets

PATIENT INFORMATION LEAFLET

Please read all of this leaflet carefully before you start to take your medicine.

This medicine has been prescribed for you personally and you should not pass it to others.

If you have any further questions, please ask your doctor or pharmacist,

The tablets are available in four strengths and contain either 2.5mg, 5mg, 10mg or 20mg active ingredient Lisinopril (as dihydrate).

The tablets also contain: mannitol, calcium hydrogen phosphate, maize starch and magnesium stearate. The 5mg, 10mg and 20mg tablets also contain the colouring agent iron oxide (E172).

The product licence holder and manufacturer is Bristol-Myers Squibb, 113 North Bridge Road, Berkenhamsted, Berkshires, United Kingdom. Phone: 01442 874000. Fax: 01442 873117. Email: info@bristolmyersquibb.co.uk

Lisinopril 2.5mg tablets PL 17907-0236, Lisinopril 5mg tablets PL 17907-0237, Lisinopril 10mg tablets PL 17907-0238

Lisinopril 20mg tablets PL 17907-0239

The tablets are round, white or almost white coloured, uncoated tablets with the markings "2.5" on one side and "BL" on the reverse, The 5mg tablets are round, light pink coloured, uncoated tablets with the markings "5" on one side and "BL" on the reverse, The 10mg tablets are round, light pink coloured, uncoated tablets with the markings "10" on one side and "BL" on the reverse, The 20mg tablets are round, pink coloured, uncoated tablets with the markings "20" on one side and "BL" on the reverse.

Lisinopril belongs to a group of medicines called ACE inhibitors that work by widening blood vessels, making it easier for the heart to pump blood through them. This helps to lower blood pressure and also help the heart to work better if it does not pump as well as required.

Lisinopril can be used for the following conditions

• To treat high blood pressure (hypertension)
• To treat heart failure
• If you have previously had a heart attack (myocardial infarction)
• To treat kidney problems caused by Type II diabetes in people with high blood pressure,

Lisinopril should not be used in children with severe kidney impairment.

The tablets are supplied to your pharmacist in packs containing 28, 30, 56, 60, 90, 120, 365 or 1000 tablets who will then provide you with the required number of tablets as prescribed by your doctor.

Before you take Lisinopril Tablets

DO NOT TAKE THIS MEDICINE: F:

• You are allergic to Lisinopril, other ACE Inhibitors (e.g. enalapril) or to any of the other ingredients in the tablets which are listed above. (An allergic reaction may be which causes swelling of the face, lips, tongue, throat or extremities, or difficulty in swallowing or breathing).

• You have ever had an allergic reaction which caused swelling of the face, lips, tongue, throat or extremities or there is a family history of this (even when this is unrelated to ACE inhibitor medicines)

• You have chronic severe kidney failure

• You suffer from narrowing of the artery to one or both kidneys

• You are suffering from cardiogenic shock (shock caused when heart fails to supply enough blood to the body).

• You have had a heart attack and your blood pressure is unstable.

• You are more than 3 months pregnant. (It is also better to avoid Lisinopril in early pregnancy - see pregnancy section.)

• You are breastfeeding

CHECK WITH YOUR DOCTOR BEFORE TAKING F:

• You suffer from heart disease or problems with narrowing of the heart valve or blood flow from the heart.

• You suffer from kidney disease or you are undergoing dialysis

• You have a narrowing (stenosis) of the kidney artery

• You have an increase in the thickness of the heart muscle (Known as hypertrophic cardiomyopathy)

• You have problems with your blood vessels (collagen vascular disease).

• You have liver problems

• You have diabetes

• You have recently had diarrhoea or vomiting (being sick)

• Your doctor has told you to control the amount of salt in your diet

• You have high levels of cholesterol and you are having a treatment called 'LDL apheresis'.

• You have had a heart attack and also suffer from kidney dysfunction.
You are to undergo a procedure to remove lipoprotein from the blood or desensitisation treatment (e.g., to reduce the allergic reaction to a bee or wasp sting).

You suffer from with your adrenal glands secreting too much of the aldosterone hormone.

You are elderly.

In Afro-Caribbean patients taking Lisinopril as the sole treatment for high blood pressure, some may have a reduced response to the medication. This may mean the dose prescribed by the doctor may need to be higher than the usual recommendations.

You must tell your doctor if you think you are (or might become) pregnant. Lisinopril is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

TAKING OTHER MEDICINES

Please tell your doctor or pharmacist if you are taking, or have recently taken any of the following medicines:

- Potassium supplements, potassium containing salt substitutes, or potassium-sparing diuretics such as amiloride, spironolactone or triamterene as these are not recommended for use in patients also taking Lisinopril.
- Water tablets (diuretic medicine).
- Medicines to break up blood clots (usually given in hospital).
- Nitrate medicines (for heart problems).
- Aspirin (Acetylsalicylic acid), if you are taking more than 3 grams each day.
- Medicines used to treat asthma.
- Medicines used to treat nose or sinus congestion or other cold remedies (including those you can buy in the pharmacy).
- Procainamide (for heart problems).
- Medicines that contain gold such as sodium aurothiomalate, which may given to you as an injection.
- Other drugs for high blood pressure e.g. beta-blockers such as atenolol, propranolol or metoprolol vasodilators such as calcium channel blockers and moxonidine or other diuretic medicines (water tablets) such as hydrochlorothiazide.
- Insulin or anti-diabetic medicines taken by mouth.
- Painkillers (non-steroidal anti-inflammatory drugs - NSAIDs) such as indomethacin, ibuprofen or aspirin.
- The drug lithium (used to treat depression) as your doctor will want you to have regular blood tests when this is taken in conjunction with Lisinopril.
- All forms (used to treat gout).
- Drugs used in the treatment of cancer or to prevent transplant rejection (immunosuppressants).
- Drugs for depression and for mental problems.

If you are taking any other medicines or supplements, including any you have bought without prescription, please check with your doctor or pharmacist before taking Lisinopril Tablets.

If you need to undergo an operation or have an anaesthetic, make sure your hospital doctor or dentist is aware you are taking Lisinopril Tablets. This is because you can get low blood pressure (hypotension) if you are given certain local or general anaesthetics while you are taking Lisinopril.

MONITORING OF PATIENTS

Your doctor may wish to check your blood pressure or kidney function regularly whilst you are taking this medicine particularly if you are elderly, have severe heart failure, have kidney problems, are dehydrated, have connective tissue disorders e.g. systemic lupus erythematosus and scleroderma, have a low immune response, are being treated with immunosuppressant drugs such as steroids, methotrexate, azathioprine or cancer treatments.

Driving Warning:

May cause dizziness or light-headedness which means you should not drive or operate machinery if affected. Also avoid alcoholic drinks as this may increase these side-effects.

Taking your medicine

Swallow the tablets whole with a drink of water. You should take the tablets as a single dose at approximately the same time each day.

The dosage of Lisinopril Tablets required is dependent on the condition being treated and varies according to the need of each individual patient. Take the tablets exactly as directed by your doctor, which will be written on the pharmacist's label. If you do not understand the directions, ask your pharmacist or doctor to explain you the same.

The usual dose is as follows:

For high blood pressure, initially, a daily dose of 10mg is recommended. The dose will gradually be increased by your doctor until control is achieved. The usual long term dose is 20mg per day.

For patients with diabetes and kidney problems the usual long term dose is 10 to 20mg per day. For patients suffering from heart failure, initially, a daily dose of 2.5mg is recommended. The usual long term dose is 5 to 20mg per day.

If you are also taking a diuretic medicine, your doctor will have either stopped this diuretic medicine or reduced its dosage for 2 to 3 days before starting your treatment with Lisinopril Tablets. The diuretic may be resumed later if this is considered necessary by your doctor.

For use after a heart attack, the initial dose is 3mg daily for 2 days, increased to 5mg daily thereafter for 6 weeks. Patients with low blood pressure may require a lower dose.
Patients with reduced renal function:
Lisinopril Tablets should be used with caution in patients with kidney problems. In those who are undergoing dialysis, the usual daily dose may be given on dialysis days, but on non-dialysis days the dose given will be dependent on the patient's blood pressure. Do not stop taking this medicine unless instructed by your doctor.

Children under 6 years: The use of Lisinopril is not recommended.

Children and adolescents aged 6 to 16 years:
The dose depends on your weight.
- For children who weigh between 20kg and 50kg, the usual starting dose is 2.5mg once a day.
- For children who weigh more than 50kg, the usual starting dose is 5mg once a day.

If you miss a dose:
Take the missed dose as soon as you remember; however, if it is almost time for your next dose, skip the missed dose and then take your next dose when it is due. Do not take a double dose to make up for missed doses.

If you take too much:
If you take too many tablets, you must obtain urgent medical attention from your doctor or hospital casualty department. The following effects are most likely to happen: Dizziness, palpitations

If you stop taking Lisinopril:
Do not stop taking your tablets, even if you are feeling unwell. Unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

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

Breastfeeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Lisinopril is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Possible Side-Effects
As with all medicines there is a possibility of unwanted effects whilst taking this medicine. Studies suggest that Lisinopril is generally well tolerated when given to hypertensive paediatric patients, but the same unwanted effects listed below for adults apply to paediatric patients.

If any of the following happens, stop taking the tablets and tell your doctor IMMEDIATELY or go to the nearest hospital casualty department.
- Swelling of your lips, tongue, throat, face, hands or feet, difficulty swallowing, shortness of breath, inflamed, red or itching skin. These are signs of a serious allergic reaction, which can occur rarely.
- Blistering of the skin, mouth, eyes or genitals.
- If you notice any of the following tell your doctor straight away:
- Sudden or severe chest pain (sign of angina or a possible heart attack), slurred speech or paralysis (signs of a possible stroke), irregular or racing heartbeat.
- Dark urine with fever and nausea or yellowing of the skin and eyes (these may be symptoms of hepatitis or jaundice)
- Abnormally low or no urine output, sudden severe vomiting and loss of appetite (this could be a sign of kidney disease or failure).

The common side-effects (affects 1 to 10 users in 100) which may occur are:
- Low blood pressure (light-headedness is a symptom)
- Headache, dizziness
- Being sick (vomiting)
- Kidney problems (show in a blood test)
- Diarrhoea
- A dry cough that does not go away

Uncommon side-effects (affects 1 to 10 users in 1,000)
- Mood changes.
- Change of colour in your fingers or toes (pale blue followed by redness) or numbness or tingling in your fingers or toes.
- Changes in the way things taste.
- Feeling sleepy.
- Spinning feeling (vertigo).
- Having difficulty sleeping.

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- Stroke.
- Fast heart beat.
- Irregular heart beat.
- Runny nose.
- Feeling sick (nausea).
- Stomach pain or indigestion.
- Skin rash or itching.
- Being unable to get an erection (impotence).
- Feeling tired or feeling weak (loss of strength).
- A very big drop in blood pressure may happen in people with the following conditions: coronary heart disease; narrowing of the aorta (a heart artery); kidney artery or heart valves; an increase in the thickness of the heart muscle. If this happens to you, you may feel dizzy or light-headed, especially if you stand up quickly.
- Changes in blood tests that show how well your liver and kidneys are working.
- Heart attack.

Rare side-effects (affects 1 to 10 users in 10,000):
- Feeling confused.
- A lumpy rash (vesicles).
- Dry mouth.
- Hair loss.
- Red patches on the skin (Psoriasis).
- Changes in the way things smell.
- Development of breasts in men.
- Condition called hypotension in which there is not enough sodium (salt) in the body.
- Sudden kidney failure.
- Increases in blood levels of bilirubin.

Very rare side-effects (affects less than 1 user in 10,000):
- Regular heartbeat of blood cells by the bone marrow, swollen lymph nodes, autoimmune disease, changes in the number and type of your blood cells. Your doctor may take blood samples from time to time to check whether Lisinopril has had any effect on your blood. The signs may include:
  - Feeling tired, pale skin, a sore throat, high temperature (fever), joint and muscle pains, swelling of the joints or glands or sensitivity to sunlight.
  - Irritability (feeling of pain and stiffness behind your cheeks and eyes).
  - wheezing.
  - Inflammation of the lungs. The signs include cough, feeling short of breath and high temperature (fever).
  - Yellowing of the skin or the whites of the eyes (jaundice).
  - Low levels of sugar in your blood (hypoglycaemia). The signs may include feeling hungry or weak, sweating and a fast heart beat.
  - Inflammation of the liver. This can cause loss of appetite, yellowing of the skin and eyes, and dark coloured urine.
  - Inflammation of the pancreas. This causes moderate to severe pain in the stomach.
  - Severe skin disorders. The symptoms include redness, blistering and peeling.
  - Passing less water (urine) than normal or passing no water.
  - Liver failure.
  - Lumps.
  - Swelling of the wall of the intestine.

Not known (frequency cannot be estimated from available data)
- Symptoms of depression.
- Fainting.

If you do notice any of the above effects, or you notice any other unusual or unexpected effects and think your tablets may be causing them, please inform your doctor or pharmacist.

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**Storing the tablets**

Keep out of the reach and sight of children.

Blister: Do not store above 25°C. Store in the original package.

Tablet Containers: Do not store above 25°C. Keep the container tightly closed.

Do not use the tablets after the expiry date shown on the carton or label.

Unless your doctor tells you to, do not keep any tablets that you no longer need. Give them back to the pharmacist.

This booklet was last revised in December 2011.
LABELLING

Lisinopril 2.5 mg Tablets (PL 17907/0236)

Carton for blisters

Braille

lisinopril
2.5 mg
tablets
### Blister foil

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*Pl holder: Bristol Laboratories Ltd.*

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**UKPAR Lisinopril 2.5, 5, 10 and 20 mg Tablets**  
PL 17907/0236-9
Lisinopril 5 mg Tablets (PL 17907/0237)

Carton for blisters

Braille

lisinopril
5 mg
tablets
Blister foil
Lisinopril 10 mg Tablets (PL 17907/0238)

Carton for blisters

Braille

lisinopril 10 mg tablets
Blister foil
Lisinopril 20 mg Tablets (PL 17907/0239)

Carton for blisters

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