

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

# Lisinopril Tablets USP

## ZESTRIL™ 2.5, 5, 10 & 20

### COMPOSITION:

Each uncoated tablet contains:

Lisinopril USP  
equivalent to anhydrous Lisinopril 2.5 mg

**Lisinopril USP**  
equivalent to anhydrous Lisinopril 5 mg  
Colour : Red Oxide of Iron

**Lisinopril USP**  
equivalent to anhydrous Lisinopril 10 mg  
Colour : Red Oxide of Iron

**Lisinopril USP**  
equivalent to anhydrous Lisinopril 20 mg  
Colour : Red Oxide of Iron

### INDICATIONS

#### Hypertension

'ZESTRIL' is indicated in the treatment of essential hypertension and in renovascular hypertension. It may be used alone or concomitantly with other classes of antihypertensive agents.

#### Congestive Heart Failure

'ZESTRIL' is indicated in the management of congestive heart failure as an adjunctive treatment with diuretics and, where appropriate, digitalis.

#### Acute Myocardial Infarction

'ZESTRIL' is indicated for the treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction, to prevent the subsequent 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.

#### Renal Complications of Diabetes Mellitus

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

### DOSAGE AND ADMINISTRATION

Since absorption of 'ZESTRIL' tablets is not affected by food, the tablets may be administered before, during or after meals. 'ZESTRIL' should be administered in a single daily dose. As with all other medication taken once daily, 'ZESTRIL' which should be taken at approximately the same time each day.

#### Essential Hypertension

In patients with essential hypertension the usual recommended starting dose is 10 mg. The usual effective maintenance dosage is 20 mg administered in a single daily dose. Dosage should be adjusted according to blood pressure response. 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.

A lower starting dose is required in the presence of renal impairment, in patients in whom diuretic therapy cannot be discontinued, patients who are volume and/or salt-depleted for any reason, and in patients with renovascular hypertension.

#### DIURETIC-TREATED PATIENTS

Symptomatic hypotension may occur following initiation of therapy with 'ZESTRIL'; 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. The diuretic should be discontinued 2 to 3 days before beginning therapy with 'ZESTRIL' (see Warnings/ Precautions). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with 'ZESTRIL' should be initiated with a 5 mg dose.

The subsequent dosage of 'ZESTRIL' should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

#### Dosage Adjustment in Renal Impairment

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

Table 1

| Creatinine Clearance (ml/min)                           | Starting Dose (mg/day) |
|---|------------------------|
| less than 10 ml/min<br>(including patients on dialysis) | 2.5 mg*                |
| 10-30 ml/min  | 2.5-5 mg               |
| 31-70 ml/min  | 5-10 mg                |

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

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

#### Renovascular Hypertension

Some patients with renovascular hypertension, especially those with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, may develop an exaggerated response to the first dose of 'ZESTRIL'. Therefore, a lower starting dose of 2.5 or 5 mg is recommended. Thereafter, the dosage may be adjusted according to the blood pressure response.

#### Congestive Heart Failure

As adjunctive therapy with diuretics and, where appropriate, digitalis, 'ZESTRIL' may be initiated with a starting dose of 2.5 mg once a day. In clinical trials doses were adjusted at 4 week intervals in patients requiring an additional therapeutic effect. Dose adjustment should be based on the clinical response of individual patients. The usual effective dosage range is 5 to 20 mg per day administered in a single daily dose.

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 'ZESTRIL'.

The effect of the starting dose of 'ZESTRIL' on blood pressure should be monitored carefully.

#### Acute Myocardial Infarction

Treatment with 'ZESTRIL' may be started within 24 hours of the onset of symptoms. The first dose of 'ZESTRIL' is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily thereafter. Patients with a low systolic blood pressure (120 mmHg or less) when treatment is started or during the first 3 days after the infarct should be given a lower dose - 2.5 mg orally (see "Warnings/ Precautions"). If hypotension occurs (systolic blood pressure less than or equal to 100 mmHg) 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 mmHg for more than 1 hour) 'ZESTRIL' should be withdrawn.

Dosing should continue for 6 weeks. Patients who develop symptoms of heart failure should continue with 'ZESTRIL' (see "Dosage and Administration" for Congestive Heart Failure). 'ZESTRIL' is compatible with intravenous or transdermal glyceryl trinitrate.

#### Renal Complications of Diabetes Mellitus

In normotensive insulin-dependent diabetes mellitus patients, the daily dose is 10 mg 'ZESTRIL' once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 75 mmHg. In hypertensive non-insulin-dependent diabetes mellitus patients, the dose schedule is as above to achieve a sitting diastolic blood pressure below 90 mmHg.

#### Paediatric Use

Safety and effectiveness of 'ZESTRIL' in children have not been established.

#### 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 (see "Dosage Adjustment in Renal Impairment") should be used to determine the starting dose of 'ZESTRIL'. Thereafter, the dosage should be adjusted according to the blood pressure response.

#### CONTRA-INDICATIONS

'ZESTRIL' is contra-indicated in patients who are hypersensitive to any component of this product, in patients with a history of angioedema relating to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

#### WARNINGS AND PRECAUTIONS

##### Symptomatic Hypotension

Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving 'ZESTRIL' 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 (see "Interactions" and "Possible Adverse Drug Reactions"). In patients with congestive 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 monitored under close medical supervision. 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 contra-indication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

As with other vasodilators, 'ZESTRIL' should be given with caution to patients with aortic stenosis or hypertrophic cardiomyopathy.

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

##### Hypotension in Acute Myocardial Infarction

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

##### Renal Function Impairment

In patients with congestive 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 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 'ZESTRIL' 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 'ZESTRIL' 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 'ZESTRIL' may be required.

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

##### Haemodialysis Patients

Anaphylactoid reactions have been reported in patients undergoing certain haemodialysis procedures (e.g. with the high flux membrane 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.

##### 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 'ZESTRIL'. In such cases, 'ZESTRIL' should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, 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 also "Contra-indications").

##### Race

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

##### 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 rechallenge.

280 MM

## 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, 'ZESTRIL' 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.

## INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER

### FORMS OF INTERACTION

#### Diuretics

When a diuretic is added to the therapy of a patient receiving 'ZESTRIL' 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 'ZESTRIL' is added. The possibility of symptomatic hypotension with 'ZESTRIL' can be minimised by discontinuing the diuretic prior to initiation of treatment with 'ZESTRIL' (see "Warnings/Precautions" and "Dosage and Administration").

#### Insulin and Oral Anti-diabetic Drugs

ACE inhibitors may potentiate the hypoglycaemic effect of insulin and oral anti-diabetic drugs.

#### Other Agents

Indomethacin may diminish the antihypertensive efficacy of concomitantly administered 'ZESTRIL'. In some patients with compromised renal function who are being treated with non steroidal anti-inflammatory drugs (NSAIDs), the co-administration of lisinopril may result in a further deterioration in renal function. 'ZESTRIL' has been used concomitantly with nitrates without evidence of clinically significant adverse interactions.

As with other drugs which eliminate sodium, lithium elimination may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are administered.

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 concomitant use of 'ZESTRIL' and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

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

## PREGNANCY AND LACTATION

### Use in Pregnancy

The use of lisinopril during pregnancy is not recommended. When pregnancy is detected, lisinopril should be discontinued as soon as possible unless it is considered life-saving for the mother. ACE inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters. Use of ACE inhibitors during this period has been associated with foetal and neonatal injury including hypotension, renal failure, hyperkalaemia and/or skull hypoplasia in the new-born. Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contracture, craniofacial deformations and hypoplastic lung development.

These adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine ACE-inhibitor exposure limited to the first trimester.

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

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

### Lactation

It is not known whether 'ZESTRIL' is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if

'ZESTRIL' is given to women who are breast feeding.

## EFFECT ON ABILITY TO DRIVE OR OPERATE MACHINERY

No specific precautions but see section "Possible Adverse Drug Reactions".

## POSSIBLE ADVERSE DRUG REACTIONS

'ZESTRIL' has been found in controlled clinical trials to be generally well tolerated. For the most part, side effects were mild and transient in nature.

The most frequent clinical side effects of 'ZESTRIL' in controlled trials were: dizziness, headache, diarrhoea, fatigue, cough and nausea. Other side effects occurring less frequently were: orthostatic effects (including hypotension), rash and asthenia.

### Hypersensitivity/Angioedema

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

Side effects which occurred rarely, either during controlled clinical trials or after the drug was marketed, include:

#### Cardiovascular

Myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see "Warnings/Precautions"). palpitations tachycardia

#### Digestive

abdominal pain and indigestion  
dry mouth  
hepatitis (hepatocellular or cholestatic)  
jaundice  
pancreatitis  
vomiting

#### Nervous System

mental confusion  
mood alterations  
paraesthesia  
vertigo  
as with other angiotensin converting enzyme inhibitors, taste disturbance, and sleep disturbances, have been reported.

#### Respiratory

bronchospasm  
rhinitis, sinusitis

## Skin

alopecia  
diaphoresis  
pruritus  
urticaria

psoriasis and severe skin disorders have been reported, including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme.

## Urogenital

impotence  
oliguria/anuria  
acute renal failure  
renal dysfunction  
uraemia

A symptom complex has been reported which may include one or more of the following:

fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leukocytosis, rash, photosensitivity or other dermatological manifestations may occur.

## Laboratory Test Findings

Clinically important changes in standard laboratory parameters were rarely associated with administration of 'ZESTRIL'. Increases in blood urea, serum creatinine, liver enzymes and serum bilirubin, usually reversible upon discontinuation of 'ZESTRIL' have been seen.

Bone marrow depression, manifest as anaemia, and/or thrombocytopenia and/or leucopenia has been reported. Agranulocytosis has been rarely reported, although a causal relationship has not been established. Rarely, haemolytic anaemia has been reported.

Small decreases in haemoglobin and haematocrit, rarely of clinical importance unless another cause of anaemia coexisted, have occurred.

Hyperkalaemia has occurred.  
Hyponatraemia has occurred.

## OVERDOSAGE

The symptoms of overdosage may include severe hypotension, electrolyte disturbance and renal failure. After ingestion of an overdose, the patient should be kept under very close supervision. Therapeutic measures depend on the nature and severity of the symptoms. Measures to prevent absorption and methods to speed elimination should be employed. If severe hypotension occurs, the patient should be placed in the shock position and an intravenous infusion of normal saline should be given rapidly. Treatment with angiotensin II (if available) may be considered. Angiotensin converting enzyme inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile dialysis membranes should be avoided. Serum electrolytes and creatinine should be monitored frequently.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic Properties

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

Whilst the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kinase 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 effects 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 and retinal tissues.

### Pharmacokinetic Properties

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. On multiple dosing lisinopril has an effective half life of accumulation of 12.6 hours.

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 bind to other serum proteins. 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. Older patients have higher blood levels and higher values for the area under the plasma concentration time curve than younger patients. Lisinopril can be removed by dialysis.

Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with interpatient variability (6-60%) at all doses tested (5-80 mg).

Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine. Lisinopril absorption is not affected by the presence of food in the gastrointestinal tract.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Angiotensin converting enzyme inhibitors may have a lesser effect on blood pressure in black hypertensive patients than in non-black hypertensive patients.

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

**Storage** : Do not store above 30°C.

### Shelf Life

Please refer to expiry date on the blister strip or outer carton.

## PRESENTATION

1. Tablets containing lisinopril dihydrate equivalent to 2.5 mg anhydrous Lisinopril.
2. Tablets containing lisinopril dihydrate equivalent to 5 mg anhydrous Lisinopril.
3. Tablets containing lisinopril dihydrate equivalent to 10 mg anhydrous Lisinopril.
4. Tablets containing lisinopril dihydrate equivalent to 20 mg anhydrous Lisinopril. (currently not available)

### Pack Size

Please refer to the outer carton for pack size.

### Date of Revision of Text

July 2003

™ Trade Mark applied for

08/JB/IN/000-045-476.2.0

For further information :  
**AstraZeneca Pharma India Limited**  
12th Mile, Bellary Road, Bangalore-560 063.

AstraZeneca

280 MM

34-170-56

SIZE : 150 x 280 MM