PROPOSED ANNOTATED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ZESTRIL® 5; ZESTRIL® 10; ZESTRIL® 20 (Tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZESTRIL 5 tablet contains: 5 mg lisinopril as the dihydrate

Each ZESTRIL 10 tablet contains: 10 mg lisinopril as the dihydrate.

Each ZESTRIL 20 tablet contains: 20 mg lisinopril as the dihydrate.

Contains sugar: mannitol 20,6 mg (ZESTRIL 5); 41,2 mg (ZESTRIL 10); 41,0 mg (ZESTRIL 20)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

ZESTRIL 5:

Round, pink, uncoated, biconvex tablet. Intagliated on one side with 5 and a heart shape, and on the other side with a bisect line.

ZESTRIL 10:

Round, pink, uncoated biconvex tablet, with "♥ 10" on one side of the tablet and plain on the other side.

ZESTRIL 20:

Round, brownish-red, uncoated biconvex tablet, with "♥ 20" on one side of the tablet and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indication

Hypertension:

ZESTRIL is indicated in the treatment of mild to moderate hypertension. It may be used alone or concomitantly with other classes of antihypertensive medicines.

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 after 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-blockers. Administration is by the oral route.

4.2 Posology and method of administration

Posology

ZESTRIL should be administered in a single daily dose. ZESTRIL should be taken at approximately the same time each day.

Absorption of ZESTRIL tablets is not affected by food, and tablets may be administered before, during or after meals.

Dosage should be adjusted according to blood pressure response.

Mild to moderate hypertension:

The recommended starting dose is 10 mg. The usual effective maintenance dosage is 20 mg administered in a single daily dose.

A maximum dose of 40 mg a day in hypertension is recommended.

If the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks on a certain dose level, the dose can further be increased.

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 in all patients who may be volume- and/or salt-depleted. The diuretic should be discontinued 2 to 3 days before beginning therapy with ZESTRIL (see section 4.4). 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:

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

Dosage in patients with renal impairment should be based on creatinine clearance as outlined below:

Creatinine clearance (ml/min)	**Starting dose (mg/day)**
31-80	5-10

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 20 mg daily.

Renovascular hypertension:

Special care to be exercised in some patients with renovascular hypertension because of the possibility of exaggerated response.

The dosage should be lowered to 2,5 mg or 5 mg and the patient should be monitored.

Congestive heart failure:

In patients not adequately controlled by digitalis and/or diuretics, ZESTRIL may be added in a starting dose of 2,5 mg once a day. Dose adjustment should be based on the clinical response of the individual patients.

The dose of ZESTRIL 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.

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, prior to therapy with ZESTRIL. The effect of the starting dosage 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 mm Hg 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 section 4.4).

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), ZESTRIL should be withdrawn.

Dosing should continue for 6 weeks. The benefit appears to be greatest in patients with large myocardial infarctions and evidence of impaired left ventricular function. Patients who develop symptoms of heart failure should continue with ZESTRIL (see section 4.2 for congestive heart failure).

ZESTRIL is compatible with intravenous or transdermal glyceryl trinitrate.

Special Populations

Use in the elderly:

There are no age-related changes in the efficacy or safety profile of the agent. When advanced age is associated with a decrease in renal function, however, the guidelines set out in the dose adjustment table (see renal impairment above) should be used to determine the starting dose of ZESTRIL. Thereafter, the dosage should be adjusted according to the blood pressure response.

Paediatric use:

Safety and effectiveness of ZESTRIL in children has not been established.

4.3 Contraindications

Nursing mothers:

The safety of ZESTRIL has not been established in nursing mothers.

ZESTRIL is contraindicated:

- Hypersensitivity to any of the components of ZESTRIL
- A history of angioedema related therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema (see section 4.4).
- Severe renal function impairment (creatinine clearance less than 30 ml/min).
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.

- Lithium therapy: Concomitant administration with ZESTRIL may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of ZESTRIL with aliskiren-containing products is contraindicated (see section 4.4)
- Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment (see section 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving ZESTRIL, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

ACE inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

ACE inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios, which may result in limb contractures, craniofacial deformities and hypoplastic lung development, as well as hypotension, renal failure, hyperkalaemia, oliguria and anuria in newborns have been reported after administration of ACE inhibitors in the second and third trimesters. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.

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

Infants whose mothers may have taken ZESTRIL should be closely observed for hypotension, oliguria and hyperkalaemia.

Lisinopril crosses the human placenta. Limited experience indicates that peritoneal dialysis may be of some benefit in the clearance of lisinopril from the neonatal circulation. Lisinopril can theoretically be removed from the neonatal circulation by exchange transfusion.

Symptomatic hypotension:

Symptomatic hypotension may occur 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. 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 these patients, 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 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.

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 mm Hg 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 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 ZESTRIL should be withdrawn.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of the RAAS through the combined use of ZESTRIL or aliskiren is therefore contraindicated (see section 4.3). ZESTRIL should not be used concomitantly with aliskiren (see section 4.3)

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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.

Renal function impairment:

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

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, 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 of ZESTRIL 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/litre and/or proteinuria exceeding 500 mg/24 hours. If renal dysfunction develops during treatment with ZESTRIL (serum creatinine concentration exceeding 265 micromol/litre or a doubling from the pre-treatment value) then the physician should consider withdrawal of ZESTRIL.

Hypersensitivity/Angio-oedema:

Angio-oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ZESTRIL. This may occur at any time during therapy. In such cases, ZESTRIL should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress,

patients may require prolonged observation since treatment with anti-histamines and corticosteroids may not be sufficient

Very rarely, fatalities have been reported due to angio-oedema 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. These patients should never receive any ACE inhibitor again.

ZESTRIL causes a higher rate of angio-oedema in black patients than in non-black patients.

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

Concomitant treatment of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril) 5 or tissue plasminogen activator may increase the risk of angioedema (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 ZESTRIL (see section 4.5).

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients undergoing certain haemodialysis procedures (e.g. with the high flux membrane AN 69 and during low-density lipoproteins

(LDL) apheresis with dextran sulphate) 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.

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.

Cough:

Cough has been reported with the use of ZESTRIL. 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.

Serum potassium:

See section 4.5..

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers.

4.5 Interaction with other medicines and other forms of interactions

Antihypertensive medicines

When combined with other antihypertensive medicines, additive falls in blood pressure may occur. Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-

system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3 and 4.4).

Medicines that may increase the risk of angioedema:

Concomitant treatment of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril) 5 or tissue plasminogen activator may increase the risk of angioedema.

Diuretics:

When a diuretic is added to the therapy of a patient receiving ZESTRIL, the antihypertensive effect is additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may 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.

Antidiabetics:

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

Lithium:

Lithium elimination may be reduced (see section 4.3).

Potassium supplements, potassium-sparing agents or potassium-containing salt substitutes and other medicines that may increase serum potassium levels:

Serum potassium tends to rise but usually remains within normal limits, however hyperkalaemia may occur. 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 and other medicines that may increase serum potassium levels (e.g., heparin, cotrimoxazole).

The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes and other medicines that may increase serum potassium levels, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

Concomitant use of ZESTRIL and any of the above-mentioned agents is contraindicated (see 4.3).

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 further deterioration in renal function.

Fluoroquinolones:

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blocker may precipitate acute kidney injury (see section 4.3).

The interaction between ACE inhibitors and fluoroquinolones to precipitate acute kidney injury is a class effect for all ACE inhibitors and class effect of all the fluoroquinolones. Thus, concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury. See Section 4.3

ZESTRIL has been used concomitantly with nitrates without evidence of clinically significant adverse interactions.

4.6 Fertility, pregnancy and lactation

The use of ZESTRIL is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take ZESTRIL during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatment which have an established safety profile for use in pregnancy. When pregnancy is detected, treatment with ZESTRIL should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spins bifida) and of kidney malformations.
ZESTRIL passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.
Oligohydramnios as well as hypotension, oliguria and anuria in new-born, have been reported after administration of ZESTRIL during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that dizziness or tiredness may occur.

4.8 Undesirable

a. Summary of the safety profile

Clinical Trials:

Common clinical side-effects of ZESTRIL are: dizziness, headache, diarrhoea, fatigue, cough and nausea. Other side-effects: orthostatic effects (including hypotension), rash and asthenia. In patients with congestive heart failure, high doses of ZESTRIL may predispose to symptoms related to hypotension (dizziness, syncope) and to biochemical changes related to impaired renal function (hyperkalaemia and increased serum creatinine) as would be expected with ACE inhibitor therapy.

b. Tabulated summary of adverse reactions

Post-marketing:

The following undesirable effects have been observed and reported during treatment with ZESTRIL with the following frequencies: Very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1000, < 1/100), rare (> 1/10000, < 1/1000), very rare (< 1/10000) including isolated reports.

Blood and the lymphatic system disorders:

very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia

Immune system disorders:

not known: anaphylactic/anaphylactoid reaction

Metabolism and nutrition disorders:

uncommon: hyperkalaemia

rare: hyponatraemia

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.

Respiratory, thoracic and mediastinal disorders:

common: cough

uncommon: rhinitis

rare: bronchospasm, sinusitis

Gastrointestinal disorders:

common: diarrhoea, vomiting

uncommon: nausea, abdominal pain and indigestion

rare: dry mouth

very rare: pancreatitis, intestinal angio-oedema

Hepato-biliary disorders:

very rare: hepatitis- either hepatocellular or cholestatic, jaundice.
Hepatic failure. Very rarely, it has been reported that in

some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving ZESTRIL who develop jaundice or marked elevation of hepatic enzymes should discontinue ZESTRIL and receive appropriate medical follow up.

Skin and subcutaneous tissue disorders:

uncommon: rash, pruritus

rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, which may be fatal, 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

General disorders and administration site conditions:

uncommon: fatigue, asthenia

Investigations:

uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes.

rare: decreases in haemoglobin, decreases in haematocrit, increases in serum bilirubin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The symptoms of overdosage may include severe hypotension, electrolyte disturbances and renal failure. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Other hypotensives

Lisinopril is an orally active ACE 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.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is also antihypertensive 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.

In patients with diabetes mellitus who have microalbuminuria, lisinopril reduces the urinary albumin excretion.

The use of ZESTRIL for the treatment of patients within 24 hours after acute myocardial infarction is based on the outcome of the GISSI-3 trial. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardico (GISSI-3) study was a multicentre, controlled, randomised, unblinded clinical trial conducted in 19 394 patients with acute myocardial infarction admitted to a coronary care unit. It was designed to examine the effects of short-term (6 week) treatment with lisinopril, nitrates, their combination, or no therapy on short-term (6 week) mortality and on longer-term death and markedly impaired cardiac function.

Patients presenting within 24 hours of the onset of symptoms who were haemodynamically stable were randomised, in a 2 x 2 factorial design, to 6 weeks of either 1) ZESTRIL alone (n = 4841), 2) nitrates alone (n = 4869), 3) ZESTRIL plus nitrates (n = 4841) or 4) open control (n = 4843). All patients received routine therapies, including thrombolytics (72 %), aspirin (84 %) and a beta-blocker (31 %), as appropriate, normally utilised in acute myocardial infarction patients.

The protocol excluded patients with hypotension (systolic blood pressure ≤ 100 mm Hg), severe heart failure, cardiogenic shock and renal dysfunction (serum creatinine > 2 mg/dl and/or proteinuria > 500 mg/24 hours). Doses of ZESTRIL were adjusted as necessary according to the protocol (see section 4.2).

Study treatment was withdrawn at 6 weeks except where clinical conditions indicated continuation of treatment.

The primary outcomes of the trial were the overall mortality at 6 weeks and a combined end-point at 6 months after the myocardial infarction, consisting of a number of patients who died, had late (day 4) clinical congestive heart failure or had extensive left ventricular damage defined as ejection fraction ≤ 35 % or an akinetic-dyskinetic [A-D] score[3] 45 %. Patients receiving ZESTRIL (n = 9646) alone or with nitrates had an 11 % lower relative risk of death (2p [2-tailed] = 0,04) compared to patients receiving no ZESTRIL (n = 9672) (619 patients [6,4 %] vs 693 patients [7,2 %] respectively, representing a 0,8 % absolute reduction in death) at 6 weeks.

The reduction in mortality at 6 months was not significant, but this was not a primary outcome measure. Although patients randomised to receive ZESTRIL for up to 6 weeks fared numerically better on the combined end-point at 6 months, the open nature of the assessment of heart failure, substantial loss to follow-up echocardiography and substantial excess use of lisinopril between 6 weeks and 6 months in the group randomised to 6 weeks of lisinopril, preclude any conclusion about this endpoint.

Patients with acute myocardial infarction, treated with ZESTRIL, had a higher (9,0 % vs 3,7 %) incidence of persistent hypotension (systolic blood pressure < 90 mm Hg for more than 1 hour) and renal dysfunction (2,4 % vs 1,1 %) in-hospital and at 6 weeks (increasing

creatinine concentration to over 3 mg/dl or a doubling or more of the baseline creatinine concentration).

5.2 Pharmacokinetic properties

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 plasma concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25 % with interpatient variability of 6-60 % over the dose range studied (5-80 mg).

The absolute bioavailability is reduced approximately 16 % in patients with heart failure. Lisinopril absorption is not affected by the presence of food.

Elimination:

ZESTRIL is excreted unchanged in the urine.

The clearance of lisinopril in healthy subjects is approximately 50 ml/min.

Upon multiple dosing, lisinopril exhibits 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.

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 is below 30 ml/min.

Pharmacokinetic parameters of lisinopril to different groups of renal patients after administration of a multiple 5 mg dose.

Renal function measured by creatinine clearance	**n**	**C_{max} (ng/ml)**	**T_{max} (hr)**	**AUC (0-24 hrs) (ng/hr/ml)**	**$t_{1/2}$ (hr)**
> 80 ml/min	6	40,3	6	492 ± 172	6,0 ± 1,1
30-80 ml/min	6	36,6	8	555 ± 364	11,8 ± 1,9
5-30 ml/min	6	106,7	8	2228 ± 938	19,5 ± 5,2

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Calcium hydrogen phosphate dihydrate

Maize starch (as anhydrous)

Pregelatinized starch (as anhydrous)

Magnesium stearate

Red iron oxide E172 CI 77491

6.2 Incompatibilities

None known

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store in a dry place at or below 25 °C. Protect from light.

6.5 Nature and contents of container

ZESTRIL is available in blister packs of 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Ltd

Building 2, Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg, 2191

South Africa

8 REGISTRATION NUMBERS

ZESTRIL 5: V/7.1.3/160

ZESTRIL 10: V/7.1.3/161

ZESTRIL 20: V/7.1.3/162

9 DATE OF FIRST AUTHORISATION

ZESTRIL 5: 9 November 1989

ZESTRIL 10: 9 November 1989

ZESTRIL 20: 9 November 1989

10 DATE OF REVISION OF THE TEXT

28 August 2023

Zestril 5	Zestril 10	Zestril 20
NAMIBIA: NS2	NAMIBIA: NS2	NAMIBIA: NS2
Reg. No.: 90/7.1.3/00293	Reg. No.: 90/7.1.3/00291	Reg. No.: 90/7.1.3/00292

Zestril 5	Zestril 10	Zestril 20
BOTSWANA: S2	BOTSWANA: S2	BOTSWANA: S2
Reg. No.: B9304860	Reg. No.: B9304865	Reg. No.: B9304870