1.5.5 PROFESSIONAL INFORMATION (AMENDED PROPOSED CLEAN)

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ZESTORETIC® 10; ZESTORETIC® 20 Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZESTORETIC 10:

Each tablet contains 10 mg lisinopril (as the dihydrate) and 12,5 mg hydrochlorothiazide.

ZESTORETIC 20:

Each tablet contains 20 mg lisinopril (as the dihydrate) and 12,5 mg hydrochlorothiazide.

Contains sugar: mannitol 17,7 mg per ZESTORETIC 10 tablet and 40 mg per ZESTORETIC 20 tablet

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

ZESTORETIC 10:

Peach-coloured, round, biconvex, uncoated tablet. Intagliated with "Zt" and "10" on one side and plain on the other.

ZESTORETIC 20:

White, round, biconvex, uncoated tablet intagliated ZESTORETIC on one side and bisected on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated in the management of mild to moderate hypertension in patients who have been stabilised on their individual components given in the same proportions.

4.2 Posology and method of administration

Posology

Essential hypertension:

The usual dosage is 1 tablet, administered once daily. ZESTORETIC should be taken at approximately the same time each day. If the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks at this dose level, the dosage may be increased to a maximum of 2 tablets, administered once daily.

Special populations

Use in the elderly:

The efficacy and tolerability of lisinopril and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

Dosage in renal insufficiency:

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

ZESTORETIC is not to be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of > 30 and < 80 ml/minute, ZESTORETIC may be used, but only after titration of the individual components.

Prior diuretic therapy:

Symptomatic hypotension may occur following the initial dose of ZESTORETIC; this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. If possible, the diuretic therapy should be discontinued for 2 to 3 days prior to initiation of therapy with ZESTORETIC, or if this is not possible, begin lisinopril alone at a low initial dose of 5 mg.

Paediatric population

Paediatric use:

Safety and effectiveness in children have not been established.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Anuria
- ZESTORETIC is contra-indicated in patients who are hypersensitive to any component of this product, in patients with a history of anaphylactic/anaphylactoid reactions or angio-oedema relating to previous treatment with an angiotensin-converting enzyme (ACE) inhibitor and in patients with hereditary or idiopathic angio-oedema (see section 4.4)
- Hypersensitivity to other sulphonamide-derived medicines.
- Pregnancy and nursing mothers (see section 4.4).
- ZESTORETIC should not be given to patients with aortic stenosis or hypertrophic cardiomyopathy.
- Concomitant use of ZESTORETIC with sacubitril/valsartan therapy. ZESTORETIC must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5).
- The concomitant use of ZESTORETIC with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR< 60 ml/min/1,73 m^2).

4.4 Special warnings and precautions for use

Pregnancy:

Should a woman become pregnant while receiving an ACE inhibitor the treatment must be stopped promptly and switched to a different medicine. Should a woman contemplate pregnancy the doctor should institute alternative medication.

Hypotension and electrolyte/fluid imbalance:

Symptomatic hypotension may occur in some patients. This is more likely in the presence of fluid or electrolyte imbalance, e.g. volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur from prior diuretic therapy, dietary salt restriction, dialysis, or during intercurrent diarrhoea or vomiting.

Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be monitored under close medical supervision.

Particular consideration should be given when therapy is administered to patients with ischaemic heart or cerebrovascular disease because 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. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

Surgery/Anaesthesia:

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Renal function impairment:

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

ZESTORETIC should not be administered to patients with renal insufficiency (creatinine clearance ≤ 80 ml/minute) until titration of the individual components has shown the need for the doses present in the combination tablet.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE 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.

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

Non-melanoma skin cancer:

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been reported in two epidemiological case control studies based on Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC although a causal relationship has not been established.

Patients taking HCTZ should be informed of the association of NMSC with HCTZ use and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and adequate protection, when exposed to sunlight, should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

Hepatic disease:

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

Hypersensitivity/Angio-oedema:

Angio-oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including ZESTORETIC. This may occur at any time during therapy. In such cases, ZESTORETIC 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.

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 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.

ZESTORETIC 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 also section 4.3).

Concomitant use of ZESTORETIC with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of ZESTORETIC. Treatment with ZESTORETIC must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ZESTORETIC with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking ZESTORETIC.

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Choroidal effusion, Acute Myopia and Angle-Closure Glaucoma:

Hydrochlorothiazide, a sulphonamide, can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Metabolic and endocrine effects:

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function (see section 4.5).

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. However, lisinopril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide.

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 reappeared upon inadvertent rechallenge.

Haemodialysis patients:

The use of ZESTORETIC is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients undergoing certain haemodialysis procedures (e.g. with the high-flux membranes 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 a different class of antihypertensive agent.

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.

4.5 Interaction with other medicines and other forms of interaction

Medicines increasing the risk of angioedema:

Concomitant use of ZESTORETIC with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use of ZESTORETIC with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increase in the risk of angioedema (see section 4.4).

Concomitant treatment with tissue plasminogen activators may increase the risk of angioedema.

Potassium supplements, potassium-sparing agents or potassium-containing salt substitutes:

The potassium losing effect of thiazide diuretics is usually attenuated by the effect of lisinopril. The use of potassium supplements, potassium-sparing agents or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If concomitant use of ZESTORETIC and any of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Lithium:

Lithium generally should not be given with diuretics or ACE inhibitors. Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the prescribing information for lithium preparations before use of such preparations.

Gold:

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Antihypertensive agents:

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

Other agents:

Indomethacin may diminish the antihypertensive efficacy of concomitantly administered hydrochlorothiazide and lisinopril. 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.

Thiazides may increase the responsiveness to tubocurarine.

When administered concurrently the following medicines may interact with thiazide diuretics:
Alcohol, barbiturates or narcotics - potentiation of orthostatic hypotension may occur.

Antidiabetic medicine (oral agents and insulin) - dosage adjustment of the antidiabetic medicine may be required.

Corticosteroids, ACTH - intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. adrenalin) - possible decreased response to pressor amines but not sufficient to preclude their use.

Non-steroidal anti-inflammatory medicine - in some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of diuretics.

4.6 Fertility, pregnancy and lactation

Pregnancy

ZESTORETIC is contraindicated in pregnancy (see section 4.3). When pregnancy is detected, ZESTORETIC should be discontinued as soon as possible (see section 4.4).

ACE-inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters.

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 deformations and hypoplastic lung development, as well as hypotension, renal failure, hyperkalaemia, oliguria and anuria in newborns have been reported after administration of ACE-inhibitors. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.

Hydrochlorothiazide hazards include foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occur in the adult.

Infants 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. There is no experience with the removal of hydrochlorothiazide, which also crosses the placenta, from the neonatal circulation.

A retrospective epidemiological study has suggested that maternal exposure to an ACE inhibitor during the first trimester of pregnancy may lead to an increased risk of malformations, particularly of the cardiovascular and central nervous systems.

Breastfeeding

It is not known whether lisinopril is secreted in human milk; however, the thiazides do appear in human milk. ZESTORETIC is not recommended for nursing mothers.

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 effects

a. **Summary of the safety profile**

Clinical trials:

The side-effects that have been observed have been limited to those reported previously with lisinopril or hydrochlorothiazide.

The most common clinical side-effects were dizziness and fatigue, which generally responded to dosage reduction.

Other side-effects were headache, dry cough and hypotension including orthostatic hypotension.

Less common were diarrhoea, nausea, vomiting, dry mouth, rash, gout, palpitations, chest discomfort, muscle cramps and weakness, paraesthesia, asthenia and impotence.

b. **Tabulated summary of adverse reactions**

Post-marketing:

The frequencies of adverse events are ranked according to the following: Very common (≥ 10%), Common (≥1/100, < 1/10); Uncommon (≥ 1/1 000, < 1/100); Rare (≥ 1/10 000, < 1/1 000); Very rare (<1/10 000).

System organ	Frequency	Event
Blood and lymphatic system disorders	Rare	Anaemia
	Very rare	Bone marrow depression, thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia
Immune system disorders	Not known	Anaphylactic/anaphylactoid reaction
Endocrine disorders	Rare	Inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders	Uncommon	Gout
	Rare	Hyperglycaemia, hypokalaemia, hyperuricaemia, hyperkalaemia
Nervous system and psychiatric disorders	Common	Dizziness, headache, paraesthesia
	Uncommon	Depressive symptoms
	Rare	Olfactory disturbance
Cardiac and vascular disorders	Common	Orthostatic effects (including hypotension), syncope
	Uncommon	Palpitations
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Common	Diarrhoea, nausea, vomiting
	Uncommon	Dry mouth
	Rare	Pancreatitis
	Very rare	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 ZESTORETIC who develop jaundice or marked elevation of hepatic enzymes should discontinue ZESTORETIC and receive appropriate medical follow up.
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis,

		and/or larynx (see section 4.3 and section 4.4).
	Very rare	Cutaneous pseudolymphoma
	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.	
Musculoskeletal and connective tissue disorders	Common	Muscle cramps
	Rare	Muscle weakness
Reproductive system and breast disorders	Common	Impotence
General disorders and administration site conditions	Common	Fatigue, asthenia
	Uncommon	Chest discomfort
Investigations	Common	Increases in blood urea, increases in serum creatinine, increases in liver enzymes, decreases in haemoglobin
	Uncommon	Decreases in haematocrit
	Rare	Increases in serum bilirubin

Other side-effects reported with the individual components alone, and which may be potential side-effects with ZESTORETIC are:

Hydrochlorothiazide: anorexia, gastric irritation, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis, vertigo, xanthopsia, leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance including hyponatraemia, muscle spasm, restlessness, transient blurred vision,

renal failure, renal dysfunction and interstitial nephritis, choroidal effusion, acute myopia and acute angle-closure glaucoma.

Lisinopril: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), tachycardia, abdominal pain and indigestion, mood alterations, mental confusion and vertigo have occurred; taste disturbance and sleep disturbance have been reported; bronchospasm, rhinitis, sinusitis, alopecia, urticaria, diaphoresis, pruritus, psoriasis and severe skin disorders, including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme, have been reported; paraesthesia, hypoaesthesia, pulmonary infiltrates, hyponatraemia, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, pancreatitis, hepatitis (hepatocellular or cholestatic) and jaundice. Infrequently, haemolytic anaemia has been reported.

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

No specific information is available on the treatment of overdosage with ZESTORETIC. Treatment is symptomatic and supportive. Therapy with ZESTORETIC should be discontinued and the patient should be kept under very close supervision. Suggested measures include induction of emesis, if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Lisinopril: The most likely features of overdosage would be hypotension, electrolyte disturbance and renal failure. Treatment is symptomatic and supportive.

Hydrochlorothiazide: The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Other hypotensives

ZESTORETIC is a combination of an angiotensin converting enzyme inhibitor (lisinopril) and a diuretic (hydrochlorothiazide) which have been used alone and concurrently for the treatment of hypertension where their effects are approximately additive.

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.

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.

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

5.2 Pharmacokinetic properties

Concomitant administration of lisinopril and hydrochlorothiazide has little effect on the pharmacokinetics of either drug. Changes that did occur in the pharmacokinetics were not clinically

relevant. Similarly, the pharmacokinetics of the combination tablet were not clinically different to concomitant administration of the separate entities.

Absorption:

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours. 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:

Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine.

On multiple dosing lisinopril has an effective half-life of accumulation of 12,6 hours. The clearance of lisinopril in healthy subjects is approximately 50 ml/ minute. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment:

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

Renal impairment:

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/minute.

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

Renal function	**n**	**C_{max} (ng/ml)**	**T_{max} (hr)**	**AUC (0-24 hrs)**	**$t_{1/2}$ (hr)**

measured by creatinine clearance				**(ng/hr/ml)**	
> 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

With a creatinine clearance of 30-80 ml/minute, mean AUC was increased by 13 %, while a 4-5 fold increase in mean AUC was observed with a creatinine clearance of 5-30 ml/minute.

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/minute.

Heart failure:

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

Elderly:

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

Hydrochlorothiazide:

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5,6 and 14,8 hours. At least 61 % of the dose is eliminated unchanged within 24 hours. After oral hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Calcium hydrogen phosphate dihydrate

Maize starch

Pregelatinized starch

Magnesium stearate

Red iron oxide E172 (CI 7491) (ZESTORETIC 10 only)

Yellow iron oxide E172 (CI 77492) (ZESTORETIC 10 only)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

ZESTORETIC 10: 24 months

ZESTORETIC 20: 36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

HDPE containers or blister packs of 30 tablets.

Not all pack sizes may be marketed

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

ZESTORETIC 10: 29/7.1.3/0652

ZESTORETIC 20: 27/7.1.3/0366

9 DATE OF FIRST AUTHORISATION

ZESTORETIC 10: 25 October 1995

ZESTORETIC 20: 15 June 1993

10 DATE OF REVISION OF THE TEXT

30 January 2022