PROFESSIONAL INFORMATION

ENPRESIL 5, 10 and 20

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ENPRESIL 5 Tablets

ENPRESIL 10 Tablets

ENPRESIL 20 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Each tablet of **ENPRESIL 5** contains 5 mg of enalapril maleate.

Each tablet of **ENPRESIL 10** contains 10 mg of enalapril maleate.

Each tablet of **ENPRESIL 20** contains 20 mg of enalapril maleate.

ENPRESIL contains sugar (lactose monohydrate).

Each tablet of **ENPRESIL 5** contains 63,875 mg of lactose monohydrate.

Each tablet of **ENPRESIL 10** contains 58,875 mg of lactose monohydrate.

Each tablet of **ENPRESIL 20** contains 117,75 mg of lactose monohydrate

This medicine contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially ‘sodium-free’.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

ENPRESIL 5: White to off white, round, flat-face beveled edge tablets with “5” embossed on one side and breakline on the other side.

ENPRESIL 10: White to off white, round, flat-face beveled edge tablets with “10” embossed on one side and breakline on the other side.

ENPRESIL 20: White to off white, round, flat-face beveled edge tablets with “20” embossed on one side and breakline on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENPRESIL is indicated in:

Hypertension

Treatment of hypertension.

Heart failure

ENPRESIL is indicated for the treatment of symptomatic congestive heart failure, in combination with diuretics and when appropriate, digitalis. In these patients **ENPRESIL** improves symptoms, increases survival, and decreases the frequency of hospitalization.

Asymptomatic Left Ventricular Dysfunction

In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction less than or equal to 35 %). **ENPRESIL** may decrease the rate of development of overt heart failure and may decrease the incidence of hospitalization for heart failure.

4.2 Posology and method of administration

Posology

Treatment for Hypertension

The initial dose is 10 mg to 20 mg depending on the degree of hypertension and is given once daily. In mild hypertension the recommended initial dose is 10 mg daily. For other degrees of hypertension the initial dose is 20 mg daily. The usual maintenance dose in one 20 mg tablet taken once daily. The dosage should be adjusted according to the needs of the patient.

Concomitant Diuretic Therapy in Hypertension

Symptomatic hypotension may occur following the initial dose of **ENPRESIL**. This is more likely in patients who are being treated currently with diuretics. Caution is recommended, therefore, since these patients may be volume or salt depleted. The diuretic therapy should be discontinued for 2 – 3 days prior to initiation of therapy with **ENPRESIL.** If this is not possible, the initial dose of **ENPRESIL** should be low (5 mg or less, see Section 4.2) to determine the initial effect on the blood pressure. Dosage should then be adjusted according to the needs of the patient.

Heart Failure/Asymptomatic Left Ventricular Dysfunction

The initial dose of **ENPRESIL** in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2,5 mg (see Section 4.2) and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with **ENPRESIL** in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient.

The dose titration may be performed over a 2 to 4 week period, or more rapidly if indicated by the presence of residual signs and symptoms of heart failure. In patients with symptomatic heart failure, this dosage regimen was effective in reducing mortality.

Blood pressure and renal function should be monitored closely before and after starting

treatment with **ENPRESIL** because hypotension and consequent renal failure have been reported. In patients treated with diuretics, the dosage should be reduced if possible before beginning treatment with **ENPRESIL**. The appearance of hypotension after the initial dose of **ENPRESIL** does not imply that hypotension will recur during chronic therapy with **ENPRESIL** and does not preclude continued use of **ENALACE**.

Serum potassium also should be monitored.

Special populations

Dosage in Renal Insufficiency

Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

Renal Status	**Creatinine Clearance ml/min**	**Initial Dose mg/day**
Mild to moderate Impairment	Less than 80, greater than 30	2,5 - 5

* See Section 4.4 **Haemodialysis Patients**.

** Enalapril is dialysable. Dosage on non-dialysis days should be adjusted depending on the blood pressure response.

Paediatric Population

The safety and efficacy of **ENPRESIL** in children has not been established.

Method of administration

ENPRESIL is administered orally with or without food.

4.3 Contraindications:

- Hypersensitivity to the active substance enalapril or any of the inactive excipients listed in section 6.1.
- The use of **ENPRESIL** is contraindicated in patients with a history of angioedema relating to previous treatment with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARBs) treatment: Such patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 ml/min).
- 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.
- Porphyria.
- Lithium therapy: Concomitant administration with **ENPRESIL** may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see section 4.4 and 4.6).
- The concomitant use of **ENPRESIL** with aliskiren-containing products is contraindicated.
- Concomitant use of fluoroquinolones with ACE inhibitors/renin-angiotensin blockers is contraindicated in patients with moderate to severe renal impairment.

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 medical practitioner should institute alternative medication.

When administered to pregnant women during the 2nd and 3rd trimesters, ACE-inhibitors can cause foetal and neonatal morbidity and mortality (see Section 4.3 and 4.6).

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 increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **ENPRESIL** and aliskiren is therefore contraindicated (see Section 4.3).

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.

Symptomatic Hypotension

In patients with uncomplicated hypertension, symptomatic hypotension may occur. In patients that have been volume- depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, hypotension is more likely to occur. Symptomatic hypotension has been observed in patients with heart failure, with or without associated renal insufficiency. In those patients with severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment, this is most likely to occur. Whenever the dose of **ENPRESIL** is adjusted in these patients, therapy should be started under medical supervision and patients should be monitored closely. Patients with ischaemic heart or cerebrovascular disease in whom excessive fall in blood

pressure could result in myocardial infarction or cerebrovascular accident should follow the same conditions.

In the event of hypotension, patients should be placed in the supine position and, if required, 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. Additional lowering of systematic blood pressure may occur with **ENPRESIL** in some patients with congestive heart failure and who have normal or low blood pressure. This is usually not a reason to discontinue treatment as this effect is anticipated. A dose reduction or discontinuation of **ENPRESIL** may be necessary if hypotension becomes symptomatic.

Renal Function Impairment

Reduced and/or less frequent doses of **ENPRESIL** may be required in patients with renal insufficiency. Routine monitoring of renal function, and careful dose titration should be done. When **ENPRESIL** has been given concomitantly with a diuretic, some patients with no apparent pre-existing renal disease have developed minor and usually transient increases in blood urea and serum creatinine. The dose of **ENPRESIL** may be required to be reduced or the diuretic may be required to be discontinued.

Hypersensitivity/Angioedema

Patients treated with angiotensin converting enzyme inhibitors, including **ENPRESIL** has reported angioedema of the face, extremities, lips, tongue, glottis and/or larynx during treatment. If this occurs, **ENPRESIL** should be discontinued immediately. The patient should be instituted and appropriately monitored to ensure complete resolution of symptoms prior to dismissing the patient. Antihistamines have been useful in relieving symptoms, although in instances where swelling has been confined to the face and lips the condition generally resolved without treatment.

Angioedema associated with laryngeal oedema may be fatal. Measures to ensure a patent

airway and appropriate therapy which may include subcutaneous epinephrine solution 1:1 000 (0,3 ml to 0,5 ml) should be administered promptly where the involvement of the tongue, glottis or are likely to cause airway obstruction.

More cases of angioedema have been reported in black patients receiving ACE – inhibitors, including **ENPRESIL** compared to non-blacks.

Whilst being treated with ACE-inhibitors, including **ENPRESIL**, patients with a history of angioedema not connected to ACE-inhibitor use, may be at increased risk of angioedema.

Anaphylactoid Reactions during Hymenoptera Desensitization

During desensitization with hymenoptera venom, patients being treated with ACE-inhibitors, including **ENPRESIL** seldom encountered life-threatening anaphylactoid reactions, by temporarily withholding ACE-inhibitor therapy before each desensitization, these reactions were avoided.

Haemodialysis Patients

Patients dialyzed with high-flux membranes (e.g., AN 69®) have reported anaphylactoid reactions when treated together with an ACE-inhibitor, including **ENPRESIL**. It should be considered to use a different type of dialysis membrane or a different class of antihypertensive medicine in these patients.

Cough

Reports of cough have been associated with the use of ACE-inhibitors, including **ENPRESIL.** The cough is characterised as 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

Enalapril blocks angiotensin II formation secondary to compensatory renin release in

patients undergoing major surgery or during anaesthesia with medicines that produce hypotension. Hypotension occurring due to this mechanism can be corrected by volume expansion.

Renovascular hypertension

ENPRESIL is contraindicated in renovascular hypertension.

(see section 4.3).

Kidney Transplantation

Treatment with **ENPRESIL** is not recommended in patients with a recent kidney transplantation due to no experience recorded.

Hepatic failure

ACE-inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and sometimes death. The mechanism of this syndrome is not understood. Discontinuation of **ENPRESIL** and an appropriate medical follow-up is recommended in patients receiving **ENPRESIL** who develop jaundice or marked elevations of hepatic enzymes.

Neutropenia/Agranulocytosis

In patients receiving ACE-inhibitors, neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported. Neutropenia occurs in patients with normal renal function and no other complicating factors. **ENPRESIL** should be used in extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. In a few cases, these patients developed serious infections which did not respond to intensive antibiotic treatment. Patients should be advised to report any sign of infection and have white blood cells periodically monitored, if **ENPRESIL** is used

in these patients.

Anaphylactoid Reactions during LDL Apheresis

During low density lipoprotein (LDL)-apheresis with dextran sulphate have patients experienced life-threatening anaphylactoid reactions. By temporarily withholding **ENPRESIL** therapy prior to each apheresis, these reactions were avoided.

Information of excipients of ENPRESIL

Lactose

ENPRESIL contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption or fructose intolerance should not take **ENPRESIL**.

4.5 Interaction with other medicinal products and other forms of interaction

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

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 (see Section 4.3 and 4.4).

Fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers

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

A case series of 16 reports of acute kidney injury (AKI) associated with enalapril and ciprofloxacin as co-suspect or interacting medicines was identified in VigiBase, the WHO global database of individual case safety reports. Analysis of 11 cases indicated that in most patients although clinical conditions and a number of medicines were likely to have increased their risk of AKI, including ACE inhibitor-related AKI, the event did not occur until

after a ciprofloxacin prescription, lending weight to ciprofloxacin being the cause or a combined action of ciprofloxacin and enalapril. Furthermore, the interaction between ACE inhibitors and fluoroquinolones to precipitate acute kidney injury is a class effect for all ACE inhibitors and not just enalapril, and also a class effect of all the fluroquinolones not just with ciprofloxacin. Thus, concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see Section 4.3).

Antihypertensive Therapy

ENPRESIL used in combination with other antihypertensive medicines, especially in combination with diuretics, may increase the antihypertensive effect.

Concomitant use of **ENPRESIL** and beta-adrenergic blocking medicines and methyldopa or calcium entry blockers, potentiates the hypotensive effects of **ENPRESIL.**

The patient should be carefully observed when **ENPRESIL** is concomitantly used with ganglionic blocking medicines or adrenergic blocking medicines.

ENPRESIL, used in combination with calcium antagonists is not recommended due to lack of experience.

Serum Potassium

Potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium containing salt substitutes, may lead to hyperkalaemia, including renal insufficiency and diabetes mellitus.

The use of **ENPRESIL** may lead to elevation of serum potassium in patients with renal failure. Increases in serum potassium may be experienced in patients with impaired renal function with the use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes. (Contraindicated, see section 4.3).

Serum Lithium

Lithium elimination may be reduced (see section 4.3).

Non-Steroidal Anti-inflammatory Drugs

The concomitant use of **ENPRESIL** and anti-inflammatory medication may result in further deterioration of renal function which is usually reversible. In occasions, especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic therapy), acute renal failure may occur.

Tricyclic Antidepressants/Antipsychotics/Anaesthetics/Narcotics

Further reduction in blood pressure may occur when **ENPRESIL** is used in combination with certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors.

Sympathomimetics

The use of sympathomimetics in combination with ACE-inhibitors may reduce the antihypertensive effects.

Antidiabetics

An increased blood-glucose-lowering effect with the risk of hypoglycaemia have been suggested in epidemiological studies with concomitant administration of ACE-inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic medicines). This seems more likely to occur in the first weeks of combined treatment and in patients with renal impairment.

Alcohol

The use of alcohol in combination with ACE-inhibitors enhances the hypotensive effect.

Acetylsalicylic acid, thrombolytics and β-blockers

The use of enalapril in combination with acetylsalicylic acid (at cardiologic doses), thrombolytics and β-blockers can be safely administered.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant **ENPRESIL** therapy.

4.6 Fertility, pregnancy and lactation

The use of **ENPRESIL** is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take **ENPRESIL** during pregnancy (see Section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with **ENPRESIL** 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.

ENPRESIL 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-borns, have been reported after administration of **ENPRESIL** 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).

Lactation

Lactation - Enalapril and enalaprilat are secreted into the breast milk. **ENPRESIL** is contraindicated in women breast-feeding their babies.

4.7 Effects on ability to drive and operate machinery

ENPRESIL may cause dizziness or weariness and should be considered when driving vehicles or operating machinery.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: Anaemia (including aplastic and haemolytic), autoimmune diseases, agranulocytosis, bone marrow depression, decreases in haematocrit, decreases in haemoglobin, lymphadenopathy, neutropenia, pancytopenia, thrombocytopenia.

Metabolism and nutrition disorders

Frequent: Hyperkalaemia.

Less frequent: Hypoglycaemia, hyponatraemia.

Nervous system and psychiatric disorders

Frequent: Depression, headache, taste alteration.

Less frequent: Dream abnormality, confusion, insomnia, nervousness, paraesthesia, sleep disorders, somnolence, vertigo

Eye disorders

Frequent: Blurred vision.

Ear and labyrinth disorders

Less frequent: Tinnitus.

Cardiac and vascular disorders

Frequent: Chest pain, dizziness, hypotension (including orthostatic hypotension), myocardial infarction or cerebrovascular accident, possible secondary to excessive hypotension in high

risk patients, rhythm disturbances, syncope, angina pectoris.

Less frequent: Flushing, orthostatic hypotension, palpitations, Raynaud's phenomenon, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders

Frequent: Cough, dyspnoea.

Less frequent: Bronchospasm/asthma, hoarseness, pulmonary infiltrates, rhinorrhoea, sore throat, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders

Frequent: Abdominal pain, diarrhoea, nausea.

Less frequent: Anorexia, constipation, dry mouth, dyspepsia, gastric irritations, glossitis, ileus, intestinal angioedema, pancreatitis, peptic ulcer, stomatitis/aphthous ulcerations, vomiting.

Hepatobiliary disorders

Less frequent: Hepatitis – either hepatocellular or cholestatic, hepatic failure, jaundice.

Skin and subcutaneous tissue disorders

Frequent: Rash, angioedema which may be fatal of the ace, extremities, lips, tongue, glottis, and/or larynx have been reported.

Less frequent: Alopecia, diaphoresis, erythema multiforme, exfoliative dermatitis, pemphigus, pruritus, Steven-Johnson syndrome, toxic epidermal necrolysis.

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive anti-nuclear antibody, elevated erythrocyte sedimentation rate, eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Musculoskeletal and connective tissue disorder

Less frequent: Muscle cramps.

Renal and urinary disorders

Less frequent: Oliguria, proteinuria, renal dysfunction, renal failure.

Reproductive system and breast disorders

Less frequent: Gynecomastia, impotence.

General disorders and administration site disorders

Frequent: Asthenia, fatigue.

Less frequent: Fever, flushing, malaise, muscle cramps, tinnitus.

Investigations

Frequent: Hyperkalaemia, increases in serum creatinine.

Less frequent: Elevations of liver enzymes, elevations of serum bilirubin, hyponatraemia, increases in blood urea.

These are usually reversible upon discontinuation of **ENPRESIL.**

Reporting of suspected adverse reactions

If you get side effects, talk to your doctor or, pharmacist or nurse. You can also report side effects 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.

Report all side effects to Unicorn Pharmaceuticals (Pty) Ltd to

enquiries@unicornpharma.co.za

4.9 Overdose

Limited data are available for overdose in humans. Hypotension is the most prominent feature of overdose reported to date. This begins some six hours after ingestion of the tablets, together with blockade of the renin-angiotensin system and stupor.

Normal saline solution administered intravenous is the recommended treatment of overdose.

Angiotensin II infusion, if available, may be beneficial. Induce emesis if ingestion is recent.

Haemodialysis may be used to remove enalapril from general circulation.

Vital signs, serum electrolytes and creatinine concentrations should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties:

Pharmacological Class: A.7.1.3 Vascular medicines – other hypotensives.

Pharmacotherapeutic group: Angiotensin Converting Enzyme (ACE) inhibitor.

ATC Code: C09AA02

ENPRESIL (enalapril maleate is the maleate salt of enalapril, a derivative of two amino acids, L-alanine and L-proline. **ENPRESIL** is hydrolysed to enalapril following oral absorption, which is specific, long-acting, non-sulphydryl angiotensin converting enzyme inhibitor.

ACE is identical to kininase II. **ENPRESIL** may block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of **ENPRESIL** remains to be elucidated.

While the mechanism through which **ENPRESIL** lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, **ENPRESIL** is antihypertensive even in patients with low-renin hypertension.

Administration of **ENPRESIL** to patients with hypertension results in a reduction of both supine and standing blood pressure without significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal

of **ENPRESIL** has not been associated with rapid increase in blood pressure.

Effective inhibition of ACE activity usually occurs 2 to 4 hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by 4 to 6 hours after administration. The duration of effect is dose-related. However, at recommended doses, antihypertensive and haemodynamic effects have been shown to be maintained for at least 24 hours.

5.2 Pharmacokinetic Properties

Absorption

Following oral administration, enalapril is rapidly absorbed with peak serum concentrations of enalapril occurring within one hour. The extent of absorption of enalapril oral tablet is approximately 60 % based on urinary recovery. Absorption is not influenced by food in the gastrointestinal tract.

Oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. After oral dose of enalapril, peak serum concentrations occur in about 4 hours. Following multiple doses of oral enalapril, the effective half-life for accumulation of oral enalapril is 11 hours, Steady-state serum concentrations of enalapril were reached after 4 days of treatment in subjects with normal renal function.

Distribution

Over the range of concentrations which are therapeutically relevant, enalaprilat binding to human plasma proteins does not exceed 60 %.

Biotransformation

There is no evidence for significant metabolism of enalapril, except for conversion to enalaprilat.

Elimination

Excretion of enalaprilat is primarily renal. Accounting for about 40 % of the dose, and intact enalapril (about 20 %), the principal components in urine are enalaprilat.

Renal impairment

In patients with renal insufficiency, the exposure of enalapril and enalaprilat is increased. In patients with mild to moderate renal insufficiency steady state AUC of enalapril was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily, AUC was increased approximately 8-fold in severe renal impairment. At this level of renal insufficiency, the effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonges and time to steady sate is delayed. Haemodialysis may be used to remove enalaprilat from the general circulation. The dialysis clearance is 62 ml/min.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients of **ENPRESIL** include: Maleic acid, lactose monohydrate, hypromellose E 464 (HPMC E 5), croscarmellose sodium and sodium stearyl fumarate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

ENPRESIL tablets are packed in white opaque, non-toxic, well thermoformable PVC film coated with PVDC on outer side.

Pack sizes:

30 tablets

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

Woodstock, Cape Town, 8001

South Africa

8 REGISTRATION NUMBER(S)

ENPRESIL 5: A 55/7.1.3/0354

ENPRESIL 10: A 55/7.1.3/0355

ENPRESIL 20: A 55/7.1.3/0356

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 14 November 2023

10 DATE OF REVISION OF THE TEXT

Not applicable