Applicant/PHCR:	Pharmaceutical Contractors (Pty) Ltd
Product proprietary name:	Hypace Tablets
Dosage form and strength:	Each tablet contains 5 mg enalapril maleate

PROPOSED PROFESSIONAL INFROMATION

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

HYPACE 5 mg (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of enalapril maleate.

Contains:

Lactose Monohydrate 10 mg

3. IDENTIFICATION PHARMACEUTICAL FORM

White to off-white, round, scored, flat bevelled tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- HYPACE is indicated in:

Hypertension: All grades of essential hypertension and renovascular hypertension.

- Heart failure: HYPACE is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients HYPACE improves symptoms, increases survival, and decreases the frequency of hospitalization (see Clinical Pharmacology section 5.2, Heart Failure, Mortality trials under section 5 for details).

Asymptomatic left ventricular dysfunction: In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction <35%), enalapril decreases the rate of development of overt heart failure

and decreases the incidence of hospitalization for heart failure (see Clinical Pharmacology section 5.2, Heart Failure, Mortality trials under Pharmacological Actions section 5 for details).

4.2 Posology and method of administration

Since its absorption is not affected by food, HYPACE tablets may be administered before, during or after meals.

Essential hypertension:

The initial dose is 10 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 is one 20 mg tablet taken once daily. The dosage should be adjusted according to the needs of the patient.

Renovascular hypertension:

Since blood pressure and renal function in such patients may be particularly sensitive to ACE-inhibition, therapy should be initiated with a lower starting dose (e.g. 5 mg or less). The dosage should then be adjusted according to the needs of the patient. Most patients may be expected to respond to one 20 mg tablet, taken once daily. For patients with hypertension who have been treated recently with diuretics, caution is recommended (See paragraph above).

Concomitant diuretic therapy in hypertension: Symptomatic hypotension may occur following the initial dose of HYPACE; 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 HYPACE. If this is not possible, the initial dose of enalapril should be low (5 mg or less) to determine the initial effect on the blood pressure. Dosage should then be adjusted according to the needs of the patient.

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 impairment	<80 >30	5
Moderate impairment	≤30 >10	2,5
Severe impairment Normally these patients will be on dialysis*	≤10	2,5 mg on dialysis days**

* See Special Precautions, Hemodialysis patients.

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

Heart failure/asymptomatic left ventricular dysfunction: The initial dose of HYPACE in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, 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 HYPACE in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg daily given as a single dose or two divided doses, as tolerated by the patient. The dose titration may be performed over two to four weeks or more rapidly in 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 HYPACE (see SPECIAL PRECAUTIONS section 4.4) because hypotension and consequent renal failure have been reported.

In patients treated with diuretics, the dose should be reduced if possible before beginning treatment with HYPACE. The appearance of hypotension after the initial dose of HYPACE does not imply that hypotension will recur during chronic therapy with HYPACE and does not preclude continued use of HYPACE. Serum potassium should also be monitored (see section 4.5).

4.3 Contraindications

Hypersensitivity to the product or any of the components and in patients with a history of angioneurotic oedema relating to previous treatment with and angiotensin converting enzyme inhibitor.

Nursing mothers: Enalapril and enalaprilat are secreted in human milk. Caution should be exercised if HYPACE is given to a nursing mother.

Aortic stenosis and hypertrophic cardiomyopathy.

Aortic stenosis and hypertrophic cardiomyopathy. The concomitant use of fluoroquinolones with ACE inhibitors / Angiotensin Receptor Blockers is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 30 ml/min) and in elderly patients.

4.4 Special warnings and precautions for use

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.

ACE-inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the 2nd and 3rd 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 deformities and hypoplastic lung development, as well as hypotension, hyperkalemia, oliguria and anuria in newborns have been reported after administration of ACE-inhibiters in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.

Infants whose mothers have taken HYPACE should be closely observed for hypotension, oliguria and hyperkalemia. These adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine ACE-inhibitor exposure limited to the first trimester.

Enalapril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit.

Symptomatic hypotension:

Symptomatic hypotension was seen in uncomplicated hypertensive patients. In hypertension patients receiving enalapril, hypotension is more likely to occur in if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see section 4.5 and Side-Effects section 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those 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, therapy should be started under medical supervision and the patient should be followed closely whenever the dose of HYPACE and/or diuretic is adjusted. Similar considerations

may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contra-indication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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

Renal Function Impaired:

Patients with renal insufficiency may require reduced and/or less frequent doses of HYPACE (see DOSAGE AND DIRECTION FOR USE section 4.2). In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and serum creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.

Some patients, with no apparent pre-existing renal disease have developed minor and usually transient increases in blood urea and serum creatinine when enalapril has been given concurrently with a diuretic. Dosage reduction of HYPACE and/or discontinuation of the diuretic may be required.

Hypersensitivity/Angioneurotic oedema:

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzymes inhibiters, including enalapril. In such cases, HYPACE should be discontinued promptly and appropriate monitoring should be taken to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although anti-histamines has been useful in relieving symptoms.

Angioneurotic oedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous epinephrine solution 1:1000 (0,3 mL to 0,5 mL) should be administered promptly.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema which receiving an ACE-inhibitor. (also see Contra-indications section 4.3)

Anaphylactic reaction during hymenoptera desensitisation:

Rarely, patients receiving ACE-inhibitors during desensitisation with hymenoptera venom have experience life threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitisation.

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g. AN 69®) and treated concomitantly with an ACE-inhibitor. In these patient's 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.

Surgery/Anaesthesia:

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

Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors / Angiotensin Receptor Blockers whether used separately and/or concomitantly.

Patients currently treated with concomitant use of ACE inhibitors / Angiotensin Receptor Blockers and fluoroquinolones should contact their doctor to re-evaluate their treatment

Lactose/fructose warning:

HYPACE 5 mg contains lactose/fructose which may have an effect on the glycaemic control of patients with diabetes mellitus.

HYPACE 5 mg contains lactose/fructose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take HYPACE 5mg.

Serum potassium: See section 4.1

Paediatric use

Enalapril has not been studied in children.

4.5 Interactions with other medicines and other forms of Interaction

Antihypertensive Therapy

The combination of HYPACE with other antihypertensive medicines may increase the antihypertensive effect, especially in combination with diuretics.

The combination of HYPACE with beta-adrenergic blocking agents and methyldopa or calcium entry blockers potentiates the hypotensive effects of enalapril.

Ganglionic blocking agents or adrenergic blocking agents, combined with HYPACE, should only be administered with careful observation of the patient.

Because of lack of experience, concomitant treatment of HYPACE with calcium antagonists is not recommended.

Serum Potassium

Risk factors for the development of hyperkaleamia 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.in patients with renal failure the administration of HYPACE may lead to elevation of serum potassium. The use of potassium supplements, potassium sparing diuretics or potassium containing salt substitute particularly in patients with impaired renal function may lead to significant increase in serum potassium. If concomitant use of the aboabove-mentionedents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Serum Lithium

The lithium elimination may be reduced. Therefore, the lithium levels of serum should be carefully compared if lithium salts are to be administered.

4.6 Fertility, pregnancy and lactation

Fertility

Should a woman contemplate pregnancy, the doctor should institute alternative medication. (see section 4.4)

Pregnancy

Should a woman become pregnant while receiving an ACE-inhibitor, the treatment must be stopped promptly and switched to a different medicine.

ACE-inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the 2nd and 3rd trimesters. ACE-inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. (see section 4.4)

Breasfeeding

Enalapril and enalaprilat are secreted in human milk. Caution should be exercised if HYPACE is given to a nursing mother.If you are breastfeeding or intend to breastfeed, consult your doctor.

4.7 Effects on ability to drive and use machines

Certain side effects that have been reported with HYPACE may affect some patients' ability to drive or operate machinery

4.8 Undesirable effects

Dizziness and headache were the more commonly reported side-effects. Other side-effects occurred and include fatigue, asthenia, hypotension, orthostatic hypotension, syncope, nausea, diarrhoea, muscle cramps, rash, cough, renal dysfunction, renal failure, and oliguria.

Hypersensitivity/angioneurotic oedema

Angioneurotic oedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx have been reported (see Special Precautions.

Cardiovascular:

- Myocardial infarction or cerebro-vascular accident, possibly secondary to excessive hypotension in high risk patients (See Special Precautions), chest pain, palpitations, rhythm disturbances, angina pectoris.

Gastrointestinal:

- Ileus, pancreatitis, hepatic failure, hepatitis –either hepatocellular or cholestatic jaundice, abdominal pain, vomiting, dyspepsia, constipation, anorexia, stomatitis.

Nervous system/Psychiatric:

- Depression, confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo.

Respiratory:

- Bronchospasm/asthma, dyspnoea, rhinorrhoea, sore throat and hoarseness pulmonary infiltrates.

Skin:

- Diaphoresis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus, pruritus, urticaria, alopecia, pemphigus.

Others:

- Impotence, flushing, taste alteration, tinnitus, glossitis, blurred vision.

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

Clinical laboratory test findings

Increases in blood urea and serum creatinine, and elevations of liver enzymes and/or serum bilirubin have been seen. These are usually reversible upon discontinuation of enalapril. Hyperkalaemia and hyponatraemia have occurred.

Decreases in haemoglobin and haematocrit have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications.

https:///www.sahpra.org.za/publications/index/8

4.9 Overdose

Limited data are available for overdosage in humans. The most prominent feature of overdosage reported to date is marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If ingestion is recent, induce emesis.

Enalapril may be removed from the general circulation by haemodialysis

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

A7.1.3 Vascular medicines - Other hypotensives.

Hypace 5 mg (enalapril maleate) is the maleate salt of enalapril, a derivative of two amino acids; L-alanine and L-proline. Following oral absorption, enalapril maleate is hydrolysed to enalaprilat which is a specific, long-acting, non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor.

5.2 Pharmacokinetic Properties

Heart Failure, Mortality trials

In a multicenter, placebo-controlled clinical trial, 2569 patients with all degrees of symptomatic heart failure and ejection fraction <35% were randomized to placebo or enalapril and followed for up to 55 months (SOLVD-Treatment). Use of enalapril was associated with an 11% reduction in all-cause mortality and a 30% reduction in hospitalization for heart failure. Diseases that excluded patients from enrolment in

the study included severe stable angina (>2 attacks/day), hemodynamically significant valvular or outflow tract obstruction, renal failure (creatinine >2,5 mg/dL), cerebral vascular disease (e.g. significant carotid artery disease), advanced pulmonary disease, malignancies, active myocarditis and constrictive pericarditis. The mortality benefit associated with enalapril does not appear to depend upon digitalis being present.

A second multicenter trial used the SOLVD protocol for study of asymptomatic or minimally symptomatic patients. SOLVD-Prevention patients, who had left ventricular ejection fraction <35% and no history of symptomatic heart failure, were randomized to placebo (n = 2117) or enalapril (n = 2111) and followed for up to 5 years. The majority of patients in the SOLVD-Prevention trial had a history of ischemic heart disease. A history of myocardial infarction was present in 80% of the patients, current angina pectoris in 34 %, and a history of hypertension in 37%. No statistically significant mortality effect was demonstrated in this population. Enalapril-treated subjects had 32% fewer first hospitalizations for heart failure, and 32% fewer total heart failure hospitalizations. Compared to placebo, 32% fewer patients receiving enalapril developed symptoms of overt heart failure. Hospitalizations for cardiovascular reasons were also reduced. There was an insignificant reduction in hospitalization for any cause in the enalapril treatment group (for enalapril vs. placebo, respectively, 1166 vs. 1201 first hospitalizations, 2649 vs. 2840 total hospitalizations), although the study was not powered to look for such an effect.

The SOLVD-Prevention trial was not designed to determine whether treatment of asymptomatic patients with low ejection fraction would be superior, with respect to preventing hospitalization, to closer follow-up and use of enalapril at the earliest sign of heart failure. However, under the conditions of follow-up in the SOLVD-Prevention trial (every 4 months at the study clinic; personal physician as needed), 68% of patients on placebo who were hospitalized for heart failure had no prior symptoms recorded which would have signalled initiation of treatment.

The SOLVD-Prevention trial was also not designed to show whether enalapril modified the progression of underlying heart disease.

In another multicenter, placebo-controlled trial (CONSENSUS) limited to patients with NYHA Class IV congestive heart failure and radiographic evidence of cardiomegaly, use of enalapril was associated with improved survival. The results are shown in the following table.

	Survival (%)	
	Six Months One Year	One Year
Enalapril (n = 127)	74	64
Placebo (n = 126)	56	48

In both CONSENSUS and SOLVD-Treatment trials, patients were also usually receiving digitalis, diuretics or both.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential and toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose Monohydrate

Microcrystalline Cell PH102

Talc Purified

Silicone Dioxide Coll Anhydrous

Croscarmellose Sodium

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C, protected from light. Keep securitainers well closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and content of the container

Packs of 28,56 or 200 tablets in securitainers and 28 or 56 tablets in blisters.

Not all pack sizes may be marked.

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Product proprietary name:	Hypace Tablets
Dosage form and strength:	Each tablet contains 5 mg enalapril maleate

6.6 Special precautions for disposal and other handling

No special requirements

7. REGISTRATION NUMBERS

33/7.1.3/0452

8. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaceutical Contractors (PTY) Ltd

44 Monteer Road

Isando

1601

9. DATE OF PUBLICATION OF THE PACKAGE INSERT AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/12/1999

10. DATE OF REVISION OF THE TEXT

To be determined