1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PHARMAPRESS 10 mg tablets

PHARMAPRESS 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of PHARMAPRESS 10 mg contains 10 mg of enalapril maleate.

Contains sugar: Lactose monohydrate 66,435 mg

Each tablet of PHARMAPRESS 20 mg contains 20 mg of enalapril maleate.

Contains sugar: Lactose monohydrate 133,246 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

PHARMAPRESS 10 mg is a round, pink tablet with bevelled edges, bisected on one side.

PHARMAPRESS 20 mg is a round, peach tablet with bevelled edges, bisected on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PHARMAPRESS is indicated in:

- **Hypertension**
  - All grades of essential hypertension;
  - renovascular hypertension.

- **Heart failure**

  PHARMAPRESS is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and when appropriate, digoxin. In these patients, PHARMAPRESS improves symptoms, increases survival and decreases the frequency of hospitalisation.

- **Asymptomatic left ventricular dysfunction**

  In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤ 35 %), PHARMAPRESS decreases the rate of development of overt heart failure and decreases the incidence of hospitalisation for heart failure.

4.2 Posology and method of administration

Posology

Adults

Essential 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 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 angiotensin converting enzyme (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 with diuretics, caution is recommended.

Concomitant diuretic therapy in hypertension

Symptomatic hypotension may occur following the initial dose of PHARMAPRESS; 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 to 3 days prior to the initiation of therapy with PHARMAPRESS. If this is not possible, the initial dose of PHARMAPRESS 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.

Special populations

Renal impairment

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

In the presence of renal impairment and in patients with congestive heart failure or patients who are currently being treated with a diuretic, a lower initial dose of PHARMAPRESS may be required.

Renal status	Creatinine clearance ml/min	Initial dose mg/day
Mild impairment	< 80 to > 30	5
Moderate impairment	≤ 30 to > 10	2,5
Severe impairment Normally, these patients will be on dialysis*	≤ 10	2,5 mg on dialysis days**

*See section 4.4

Haemodialysis 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 PHARMAPRESS in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is one tablet of PHARMAPRESS 2,5 mg daily and it should be administered under close medical supervision to determine the initial effect on blood pressure. In the absence of, or after effective management of symptomatic hypotension following initiation of therapy with PHARMAPRESS in congestive heart failure, the dose should be gradually increased, depending on the patient's response to the usual maintenance dose (10 mg to 20 mg) in a single or divided dose.

This 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 is effective in reducing mortality.

Blood pressure and renal function should be monitored closely before and after starting treatment with PHARMAPRESS (see section 4.4) 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 PHARMAPRESS. The appearance of hypotension after the initial dose of PHARMAPRESS does not imply that hypotension will recur during chronic therapy with PHARMAPRESS and does not preclude continued use of PHARMAPRESS.

Paediatric population

The safety and efficacy of PHARMAPRESS in children have not been established (see section 4.4 below).

Method of administration

For oral administration.

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

4.3 Contraindications

PHARMAPRESS is contraindicated in:

- Patients with hypersensitivity to enalapril, to any other ACE inhibitor or to any of the excipients in PHARMAPRESS (see section 6.1).
- Patients with a history of angioedema relating to previous treatment with an angiotensin-converting enzyme (ACE) inhibitor or Angiotensin receptor blockers (ARBs).
  These patients must never again be given these medicines.
- Concomitant use with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see sections 4.4 and 4.5).
- Concomitant use with sacubitril/valsartan therapy. PHARMAPRESS must not be initiated earlier than 36 hours after the last dose of sacubitril/ valsartan (see sections 4.4 and 4.5).

- Patients with hereditary or idiopathic angioedema.
- Patients with hypertrophic obstructive cardiomyopathy (HOCM).
- Patients with severe renal function impairment (creatinine clearance less than 30 ml/min).
- Patients with bilateral renal artery stenosis.
- Patients with renal artery stenosis with a single kidney.
- Patients with aortic stenosis.
- Concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene and amiloride (see section 4.4 and 4.5).
- Concomitant use with fluoroquinolones in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 ml/ml) and in elderly patients (see section 4.4 and 4.5).
- Concomitant administration of lithium with PHARMAPRESS may lead to toxic blood concentrations of lithium (see section 4.4 and 4.5).
- Patients with porphyria.
- Pregnancy and lactation (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving PHARMAPRESS, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine with an established safety profile for use in pregnancy (see section 4.3 and 4.6).

Should a woman contemplate pregnancy, the doctor should consider an alternative class of medicine.

PHARMAPRESS should not be initiated during pregnancy.

Use of PHARMAPRESS is not recommended during breastfeeding (see section 4.6)

Symptomatic hypotension

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving PHARMAPRESS, symptomatic hypotension is most likely to occur if the patient has been volume depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see section 4.5 and 4.8). 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, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of PHARMAPRESS 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 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 contraindication 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 PHARMAPRESS. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of PHARMAPRESS may be necessary.

Aortic or mitral valve stenosis/hypertrophic cardiomyopathy

As with all vasodilators, ACE inhibitors, such as enalapril, as in PHARMAPRESS, should be

given with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal function impairment

Patients with renal impairment (creatinine clearance <80 mL/min) may require reduced and/or less frequent doses of PHARMAPRESS. The initial PHARMAPRESS dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.

Renal failure has been reported in association with enalapril, as in PHARMAPRESS, and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with enalapril, as in PHARMAPRESS is usually reversible.

Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and serum creatinine when PHARMAPRESS has been given concomitantly with a diuretic. Dosage reduction of PHARMAPRESS and/or discontinuation of the diuretic may be required. The situation should raise the possibility of underlying renal artery stenosis.

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors, such as enalapril, as in PHARMAPRESS. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under

close medical supervision with low doses, careful titration, and monitoring of renal function.

Kidney transplantation

There is no experience regarding the administration of PHARMAPRESS in patients with a recent kidney transplantation. Treatment with PHARMAPRESS is therefore not recommended.

Hepatic failure

Rarely, ACE inhibitors, such as enalapril, as in PHARMAPRESS, 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. Patients receiving PHARMAPRESS who develop jaundice or marked elevations of hepatic enzymes should discontinue PHARMAPRESS and receive appropriate medical follow-up.

Neutropenia/agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, such as enalapril, as in PHARMAPRESS. Neutropenia usually only occurs in patients with abnormal renal function and other complicating factors.
PHARMAPRESS should be used with 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. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If PHARMAPRESS is used in such patients, periodic monitoring of white blood cell counts is advised, and patients should be instructed to report any sign of infection.

Hypersensitivity/angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including PHARMAPRESS.

This may occur at any time during treatment. In such cases, PHARMAPRESS should be discontinued promptly, and appropriate 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 antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema 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. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy such as subcutaneous epinephrine (adrenaline) solution 1: 1 000 (0,3 ml to 0,5 ml) and/or measures to ensure the patient's airway, should be administered promptly.

Black patients receiving ACE inhibitors, such as enalapril, as in PHARMAPRESS, have been reported to have a higher incidence of angioedema compared to non-black patients.

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

Concomitant use of fluoroquinolones

Concomitant use of fluoroquinolones and PHARMAPRESS may precipitate acute kidney injury (AKI) 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 PHARMAPRESS, whether used separately and/or concomitantly (see section 4.3 and 4.5).

Concomitant use of sacubitril/ valsartan

Concomitant use of PHARMAPRESS 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 enalapril. Treatment with PHARMAPRESS must not be initiated earlier than 36 hours after the last dose of sacubitril/ valsartan (see section 4.3 and 4.5).

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Concomitant use of PHARMAPRESS with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.8). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking PHARMAPRESS.

Anaphylactoid reactions during hymenoptera desensitisation

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

Anaphylactoid reactions during LDL apheresis

Patients receiving ACE inhibitors, such as enalapril, as in PHARMAPRESS, during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions can be avoided by temporarily withholding

PHARMAPRESS therapy prior to each apheresis.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g. AN 69®) and treated concomitantly with PHARMAPRESS. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive medicine.

Hypoglycaemia

Diabetic patients treated with oral antidiabetic agents or insulin starting PHARMAPRESS, should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see section 4.5).

Cough

Cough has been reported with the use of PHARMAPRESS. 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 medicines that produce hypotension, PHARMAPRESS 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.

Serum potassium (hyperkalaemia)

PHARMAPRESS can cause hyperkalaemia because it inhibits the release of aldosterone. The

effect is usually not significant in patients with normal renal function. However, risk factors for the development of hyperkalaemia include in those with renal impairment, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonist or angiotensin receptor blockers (ARBs). In patients with renal failure, the administration of PHARMAPRESS may lead to elevation of serum potassium. The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal dysrhythmias. Concomitant use of the above-mentioned medicines with PHARMAPRESS is contraindicated (see section 4.3 and 4.5).

Lithium

Concomitant administration of lithium with PHARMAPRESS is contraindicated (see section 4.3 and 4.5).

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

There is evidence that the concomitant use of ACE-inhibitors, such as enalapril, as in PHARMAPRESS, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, ARBs or aliskiren is therefore contraindicated (see section 4.3 and 4.5).

ACE-inhibitors such as PHARMAPRESS and ARBs should not be used concomitantly in patients with diabetic nephropathy.

Ethnic differences

As with other ACE inhibitors, enalapril, as in PHARMAPRESS is apparently less effective in lowering blood pressure in the black population than in the non-black population, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Paediatric use

The safety and efficacy of PHARMAPRESS in children have not been established (see section 4.2 above).

Excipients

PHARMAPRESS contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance total lactase deficiency, or glucose-galactose malabsorption should not take PHARMAPRESS.

4.5 Interaction with other medicines and other forms of interaction

Medicines increasing the risk of angioedema

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

Concomitant use of PHARMAPRESS with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (section 4.4).

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

Dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse event

such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to use of a single RAAS-acting medicine (see section and 4.4).

Fluoroquinolones

Concomitant use of fluoroquinolones and PHARMAPRESS may precipitate acute kidney injury (AKI) (see section 4.3 and 4.4).

The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with enalapril as in PHARMAPRESS. Potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increase in serum potassium. Care should also be taken when enalapril as in PHARMAPRESS is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/ sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of enalapril, as in PHARMAPRESS, with the above-mentioned medicines is not recommended.

Ciclosporin

Hyperkalaemia may occur during concomitant use of PHARMAPRESS with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of PHARMAPRESS with heparin. Monitoring of serum potassium is recommended.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with PHARMAPRESS (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of PHARMAPRESS.

Other antihypertensive medicines

The combination of PHARMAPRESS with other antihypertensive medicines may increase the hypotensive effects of PHARMAPRESS.

Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

The combination of PHARMAPRESS with beta-adrenergic blocking medicines and methyldopa or calcium entry blockers potentiates the hypotensive effects of PHARMAPRESS.

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

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

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, such as enalapril, as in

PHARMAPRESS. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with PHARMAPRESS. Use of PHARMAPRESS with lithium is contraindicated, careful monitoring of serum lithium levels should be performed (see section 4.4).

Tricyclic antidepressants/antipsychotics/anaesthetics/narcotics

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE inhibitors, such as enalapril, as in PHARMAPRESS, may result in further reduction of blood pressure (see section 4.4).

Non-steroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive medicines, including PHARMAPRESS. Therefore, the antihypertensive effect of ARBs or ACE inhibitors such as PHARMAPRESS may be attenuated by NSAIDs including selective COX-2 inhibitors.

The co-administration of NSAIDs (including COX-2 inhibitors) and ACE inhibitors such as PHARMAPRESS exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Acute renal failure may occur, especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic therapy). Therefore, the combination should be administered with caution in patients with compromised renal function. Patients should be adequately hydrated, and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter.

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 ACE inhibitor therapy including enalapril, as in PHARMAPRESS.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors, such as enalapril, as in PHARMAPRESS.

Antidiabetics

Concomitant administration of ACE inhibitors such as PHARMAPRESS and antidiabetic medicines (insulins, oral hypoglycaemic medicines) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appears to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. (See section 4.4 and 4.8).

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors, such as enalapril, as in PHARMAPRESS.

Acetylsalicylic acid, thrombolytics and beta-blockers

PHARMAPRESS can be safely administered concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics and beta-blockers.

4.6 Fertility, pregnancy and lactation

The use of PHARMAPRESS is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

The use of PHARMAPRESS is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take PHARMAPRESS 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 PHARMAPRESS should be stopped immediately and if appropriate, alternative therapy should be started.
PHARMAPRESS can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters. 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.

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

Should exposure to ACE inhibitors, as in PHARMAPRESS have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken PHARMAPRESS should be closely observed for hypotension, oliguria and hyperkalaemia. These adverse effects to the embryo and foetus do

not appear to have resulted from intra-uterine PHARMAPRESS exposure limited to the first trimester.

PHARMAPRESS, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit (see section 4.4).

Breastfeeding

Enalapril as in PHARMAPRESS is excreted into breast milk. Mothers breastfeeding their infants should not be treated with PHARMAPRESS (see section 4.3).

Fertility

No data available.

4.7 Effects on ability to drive and use machines

PHARMAPRESS has minor on the ability to drive or operate machinery.

Since adverse reactions such as dizziness, somnolence and blurred vision have been reported in patients taking PHARMAPRESS, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that PHARMAPRESS does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

a) Tabulated list of adverse reactions

System organ class	Frequent	Less Frequent	Frequency unknown
Blood and the lymphatic system disorders		Anaemia (including aplastic and haemolytic). neutropenia, decreases in haemoglobin, decreases in	

		haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy	
Immune system disorders	Hypersensitivity of the face, (which may be fatal), extremities, lips, tongue, glottis and/or larynx	Autoimmune diseases, angioedema	A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive antinuclear antibody (ANA), elevated erythrocyte sedimentation rate (ESR), eosinophilia and leucocytosis.
Endocrine disorders			Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Hyperkalaemia	Hyponatraemia, hypoglycaemia,	
Psychiatric disorders	Depression	Confusion, nervousness, insomnia, dream abnormality, sleep disorders, somnolence	
Nervous system disorders	Dizziness, headache, syncope, taste alteration	Paraesthesia, vertigo	
Eye disorders	Blurred vision		
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders	Chest pain, rhythm disturbances, angina pectoris, tachycardia	Palpitations, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients	
Vascular disorders	Hypotension (including orthostatic hypotension)	Flushing, Raynaud's phenomenon	

Respiratory, thoracic and mediastinal disorders	Cough, dyspnoea	Rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma, pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilia pneumonia	
Gastrointestinal disorders	Nausea, diarrhoea, abdominal pain	Ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, stomatitis, glossitis, gastric irritations, dry mouth, peptic ulcer, /aphthous ulcerations, intestinal angioedema	
Hepato-biliary disorders		Hepatic failure, hepatitis (either hepatocellular or cholestatic including necrosis), cholestasis jaundice.	
Skin and subcutaneous tissue disorders	Rash	Diaphoresis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome toxic epidermal necrolysis pruritus, urticaria, alopecia, pemphigus, erythroderma	Photosensitivity or other dermatologic manifestations
Musculoskeletal, connective tissue and bone disorders		Muscle cramps	
Renal and urinary disorders		Renal dysfunction, renal failure, oliguria, proteinuria,	
Reproductive system and breast disorders		Impotence, gynaecomastia	
General disorders and administrative site conditions	Asthenia, fatigue	Malaise, fever	
Investigations	Increases in serum creatinine	Increases in blood urea, elevations of liver enzymes, elevations of 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. Healthcare 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

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/<+27 (0)11 239-6200

4.9 Overdose

Symptoms

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. Symptoms associated with overdosage of ACE inhibitors, such as enalapril, as in PHARMAPRESS, may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum enalaprilat levels 100 times and 200 times higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril, as in PHARMAPRESS, respectively.

Treatment

The recommended treatment of overdosage is intravenous infusion of saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g. emesis, administration of absorbents, and sodium sulphate). Enalaprilat may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored

continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Vascular medicines – other hypotensives

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors, plain

ATC code: C09AA02

Mechanism of action

Enalapril maleate is the maleate salt of enalapril, a derivative of two amino acids, L-alanine and L-proline. Following oral absorption, enalapril (a prodrug) is hydrolysed to, enalaprilat, which is a specific, long-acting, non-sulphydryl angiotensin converting enzyme (ACE) inhibitor. ACE is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance angiotensin II.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

5.2 Pharmacokinetic properties

Absorption

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril is approximately 60 %.

The absorption of oral enalapril is not influenced by the presence of food in the gastrointestinal tract.

Distribution

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Similar peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril.

Elimination

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40 % of the dose, and intact enalapril. Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE. In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of oral enalapril. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PHARMAPRESS 10 mg

FD&C blue/indigo carmine lake (C.I. 73015), FD&C yellow/sunset yellow FCF lake (C.I. 15985), lactose monohydrate, ponceau 4R lake (C.I. 16255), starch maize, zinc stearate

PHARMAPRESS 20 mg

Alumina, indigo carmine lake (C.I. 73015), lactose monohydrate, sodium chloride, sodium sulphate, starch maize, sunset yellow FCF lake (C.I. 15985), zinc stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

28 or 30 tablets are packed in a polyamide, aluminium and polyvinylchloride film sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton.

Not all pack sizes are necessarily marketed.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

PHARMAPRESS 10 mg: 33/7.1.3/0479

PHARMAPRESS 20 mg: 33/7.1.3/0480

9. DATE OF FIRST AUTHORISATION

Dates of registration:

PHARMAPRESS 10 mg: 27 June 2000

PHARMAPRESS 20 mg: 27 June 2000

10 DATE OF REVISION OF TEXT

05 January 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

Namibia:	NS2
PHARMAPRESS 10 mg:	04/7.1.3/0112
PHARMAPRESS 20 mg:	04/7.1.3/0121

ZA_PHARMCOMB_2401_00