## 1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

**SCHEDULING STATUS**

**S3**

## 1. NAME OF THE MEDICINE

**PHARMAPRESS CO** 20,0/12,5 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of PHARMAPRESS CO contains 20,0 mg of enalapril maleate and 12,5 mg of hydrochlorothiazide.

Contains sugar: Lactose monohydrate 130,50 mg

For full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Tablets

A round, white to off-white biconvex tablet.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PHARMAPRESS CO is indicated for the treatment of hypertension in patients where fixed combination therapy is considered more appropriate than monotherapy.

### 4.2 Posology and method of administration

**Posology**

**Hypertension**

The usual dose is one tablet, administered once daily. The dosage may be increased to a maximum of two tablets, administered once daily, if appropriate.

**Special populations**

*Renal impairment*

For patients with renal impairment, thiazides, including hydrochlorothiazide, as in PHARMAPRESS CO, may not be the appropriate diuretic for use and are ineffective at creatinine clearance values of 30 mL/min or below (i.e. moderate or severe renal insufficiency).

In any patient with renal insufficiency, PHARMAPRESS CO must not be used as initial therapy.

PHARMAPRESS CO may be used in patients with creatinine clearance of > 30 mL/min and < 80 mL/min, but only after titration of the individual components (see section 4.3).

**Paediatric population**

No data are available.

**Method of administration**

PHARMAPRESS CO is taken orally.

**4.3 Contraindications**

PHARMAPRESS CO is contraindicated in:

- Patients with hypersensitivity to enalapril maleate, hydrochlorothiazide, other sulphonamide derived medicines, or any of the excipients in PHARMAPRESS CO (see section 6.1).
- Patients with a history of angioneurotic oedema relating to previous treatment with an

ACE-inhibitor or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines.

- 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) or anuria.
- Patients with bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Patients with aortic stenosis.
- Patients with severe hepatic impairment.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, eplerenone, triamterene and amiloride (see section 4.5).
- Patients with Addison's disease.
- Concomitant therapy with lithium. Administration of lithium with PHARMAPRESS CO may lead to toxic blood concentrations of lithium (see section 4.5).
- Concomitant use of PHARMAPRESS CO with aliskiren-containing medicines in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 $m^2$) (see section 4.5).
- Concomitant use of PHARMAPRESS CO with fluoroquinolones in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients (see section 4.5).
- Combination with sacubitril/valsartan due to the increased risk of angioedema. Do not administer PHARMAPRESS CO within 36 hours of switching to or from sacubitril/valsartan, a medicine containing a neprilysin inhibitor (see sections 4.4 and 4.5).

- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.
- Pregnancy and lactation (see section 4.6).

**4.4 Special warnings and precautions for use**

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| Should a woman become pregnant while receiving PHARMAPRESS CO, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6) |

ACE inhibitors, such as enalapril, as in PHARMAPRESS CO, should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

*Hypersensitivity/angioedema*

Angioedema of the extremities, face, lips, glottis and/or larynx and tongue has been reported. PHARMAPRESS CO should be discontinued promptly in such cases and appropriate monitoring should be instituted to ensure complete resolution of symptoms. The condition may resolve without treatment, in those instances where swelling has been confined to the face and lips, although antihistamines have been useful in relieving symptoms. 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.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the glottis, larynx or the tongue, likely to cause airway obstruction, especially those with

a history of airway surgery, appropriate therapy such as intravenous epinephrine solution 1:1 000 (0,3 ml to 0,5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Patients from the black ethnicity group receiving ACE inhibitors, such as enalapril, as in PHARMAPRESS CO, have been reported to have a higher incidence of angioedema compared to white patients. However, in general it appears that black patients have an increased risk for angioedema.

Patients with a history of angioedema unrelated to ACE inhibitor therapy, may be at increased risk of angioedema, while taking an ACE inhibitor, such as enalapril, as in PHARMAPRESS CO (see section 4.3).
Patients receiving co-administration of an ACE inhibitor, such as enalapril, as in PHARMAPRESS CO, and mTOR (mammalian target of rapamycin) inhibitor (e.g. temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema.

In patients receiving thiazides, such as hydrochlorothiazide, as in PHARMAPRESS CO, sensitivity reactions may occur with or without a history on bronchial asthma or allergy. The use of thiazides such as hydrochlorothiazide, as in PHARMAPRESS CO, has been reported to activate or exacerbate systemic lupus erythematosus (SLE).

*Anaphylactoid reactions during hymenoptera desensitisation*
Patients receiving ACE inhibitors, such as enalapril, as in PHARMAPRESS CO, during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions are avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

*Anaphylactoid reactions during LDL-Apheresis*

Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactic reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

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

There is evidence that the concomitant use of ACE-inhibitors, 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 PHARMAPRESS CO and aliskiren is therefore contraindicated. PHARMAPRESS CO should not be used concomitantly with aliskiren (see section 4.3). ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

*Hypotension and electrolyte fluid imbalances*

In some patients, symptomatic hypotension may occur. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. hyponatremia, hypochloraemic alkalosis, volume depletion, hypokalaemia or hypomagnesaemia. This may occur during intercurrent diarrhoea or vomiting, due to dietary salt restriction or diuretic therapy, including hydrochlorothiazide, as in PHARMAPRESS CO.

Warning signs of fluid or electrolyte imbalance are xerostomia, thirst, weakness, lethargy, somnolence, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. At appropriate intervals, periodic determination of serum electrolytes should be performed in such patients.

Although hypokalaemia may develop during use of thiazide diuretics, such as hydrochlorothiazide, as in PHARMAPRESS CO, concurrent therapy with enalapril, as in PHARMAPRESS CO may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).
Hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does not usually require treatment. Hydrochlorothiazide, as in PHARMAPRESS CO, may increase the urinary excretion of magnesium, which may result in hypomagnesemia.
Symptomatic hypotension may occur mainly after the first dose of PHARMAPRESS CO; this is more likely in patients who have received prior diuretic therapy. Prior to initial therapy with PHARMAPRESS CO, diuretic therapy should be discontinued for 2 to 3 days. When therapy is administered to patients with ischaemic heart or cerebrovascular disease, particular consideration should be given, because an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
In hypertensive patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been documented. 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 CO and/or diuretic is adjusted.

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, including enalapril, as in PHARMAPRESS CO (see section 4.3).

The patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline if hypotension occurs. A transient hypotensive response is not a contraindication to further doses. Following the 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.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with PHARMAPRESS CO. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or PHARMAPRESS CO may be necessary.

*Aortic stenosis and hypertrophic cardiomyopathy*

As with all vasodilators, ACE-inhibitors, such as enalapril, as in PHARMAPRESS CO, 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 (see section 4.3).

*Renal function impairment*

(see Dosage in renal insufficiency under section 4.2)

There is an increased risk of renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, are treated with ACE-inhibitors, such as enalapril, as in PHARMAPRESS CO. Loss of renal function may occur with only mild changes in serum creatinine (see section 4.3). In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function. When PHARMAPRESS CO has been given concomitantly with a

diuretic, some hypertensive patients, with no apparent pre-existing renal disease have developed minor increases in serum creatinine and blood urea. The combination should be discontinued, if this occurs during therapy with PHARMAPRESS CO. This situation should raise the possibility of underlying renal artery stenosis.

Renal failure has been reported in association with enalapril, as in PHARMAPRESS CO, 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 CO, is usually reversible.

PHARMAPRESS CO should not be administered to patients with renal insufficiency (creatinine clearance < 80 mL/min and > 30 mL/min) until titration of enalapril has shown the need for the dose present in this formulation (see section 4.2).

Hydrochlorothiazide, as in PHARMAPRESS CO, may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 mL/min or below (i.e. moderate or severe renal insufficiency) (see sections 4.3 and 4.2).

The use of enalapril, as in PHARMAPRESS CO, is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes and treated concomitantly with an ACE inhibitor, such as enalapril, as in PHARMAPRESS CO.

In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive medicine.
There is no experience regarding the administration of enalapril, as in PHARMAPRESS

CO, in patients with a recent kidney transplantation. Treatment with PHARMAPRESS CO is therefore not recommended.

Concomitant use of fluoroquinolones and PHARMAPRESS CO may precipitate acute kidney injury (AKI) in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.4). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or PHARMAPRESS CO whether used separately and/or concomitantly (see sections 4.3 and 4.5).

*Hyperkalaemia*

The combination of enalapril and a low-dose diuretic, such as hydrochlorothiazide, as in PHARMAPRESS CO, cannot exclude the possibility of hyperkalaemia to occur.

Elevations in serum potassium have been documented in some patients treated with ACE-inhibitors, including enalapril, as in PHARMAPRESS CO.

Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, inter-current events in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin).

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. If concomitant use of enalapril, as in PHARMAPRESS CO, and any of the

above-mentioned medicines is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

*Hepatic disease*

Thiazides, such as hydrochlorothiazide, as in PHARMAPRESS CO, 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 and hepatic encephalopathy (see sections 4.3).

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

*Surgery/anaesthesia*

Enalapril, as in PHARMAPRESS CO, blocks angiotensin II formation and therefore impairs the ability of patients undergoing major surgery or during anaesthesia with medicines that produce hypotension to compensate via the renin-angiotensin system. Volume expansion can correct hypotension considered to be due to this mechanism.

*Metabolic and endocrine effects*

Glucose tolerance may be impaired by thiazide therapy, including therapy with hydrochlorothiazide, as in PHARMAPRESS CO. It may be required that dosage of antidiabetic medicines, including insulin is adjusted. Diabetic patients treated with oral antidiabetic medicine or insulin starting an ACE inhibitor, such as enalapril, as in PHARMAPRESS CO, should be told to closely monitor for hypoglycaemia, especially during the first month of combined use.

Hydrochlorothiazide, as in PHARMAPRESS CO, may decrease serum sodium, magnesium and potassium levels.

Urinary calcium excretion may be decreased by thiazides, such as hydrochlorothiazide, as in PHARMAPRESS CO. Intermittent and slight elevation of serum calcium may be caused by thiazides, such as hydrochlorothiazide, as in PHARMAPRESS CO. Marked hypercalcinaemia may be evidence of hidden or latent hyperparathyroidism. Before carrying out tests for parathyroid function, PHARMAPRESS CO should be discontinued.

Increases in triglyceride and cholesterol levels may be associated with thiazide diuretic therapy, including therapy with hydrochlorothiazide, as in PHARMAPRESS CO. At the 12,5 mg dose of hydrochlorothiazide, as in PHARMAPRESS CO, minimal or no effect has been documented.
Thiazide therapy, including therapy with hydrochlorothiazide, as in PHARMAPRESS CO, may precipitate gout and/or hyperuricemia in certain patients. This effect on hyperuricemia appears to be dose-related. Urinary uric acid may additionally be increased by enalapril, as in PHARMAPRESS CO, and the hyperuricemia effect of hydrochlorothiazide, as in PHARMAPRESS CO, may thus be attenuated.

*Cough*

Cough has been reported with the use of ACE inhibitors such as enalapril, as in PHARMAPRESS CO. Characteristically, the cough is persistent and non-productive and resolves after discontinuation of therapy. ACE-inhibitor induced cough should be considered as part of the differential diagnosis of cough.

*Neutropenia/agranulocytosis*

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, such as enalapril, as in PHARMAPRESS CO. In patients with normal renal function and no other complicating factors, neutropenia occurs infrequently. Enalapril, as in PHARMAPRESS CO, should be used with extreme caution in patients with collagen vascular disease, during immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Patients may develop serious infections which may not respond to intensive antibiotic therapy. If PHARMAPRESS CO 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.

*Ethnic differences*

As with other ACE inhibitors, enalapril, as in PHARMAPRESS CO, 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.

*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), as in PHARMAPRESS CO, exposure has been observed in two epidemiological studies. Photosensitizing actions of hydrochlorothiazide, as in PHARMAPRESS CO, could act as a possible mechanism for NMSC. Patients taking PHARMAPRESS CO should be informed of the risk of NMSC 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 UV rays and, in case of exposure, adequate protection should be advised to the patients to minimise the risk of skin cancer. Suspicious skin

lesions should be promptly examined, potentially including histological examinations of biopsies. PHARMAPRESS CO should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

*Lithium*

The combination of lithium with enalapril and diuretic medicines, including hydrochlorothiazide, as in PHARMAPRESS CO, is generally not recommended (see sections 4.3 and 4.5).

*Anti-doping test*

Hydrochlorothiazide, as in PHARMAPRESS CO, can produce a positive analytic result in an anti-doping test.

*Choroidal effusion, acute myopia and secondary angle-closure glaucoma*

Sulfonamide or sulfonamide derivative medicines, such as hydrochlorothiazide, as in PHARMAPRESS CO, 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 medicine 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 sulfonamide or penicillin allergy.

**Paediatric population**

The safety and efficacy in children have not been established.

*Use in the elderly*

The tolerability and efficacy of enalapril maleate and hydrochlorothiazide, administered concomitantly, as in PHARMAPRESS CO, were similar in both elderly and younger hypertensive patients.

*Excipients*

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

**4.5 Interaction with other medicines and other forms of interaction**

*Other antihypertensive therapy*

Adrenergic blocking medicines or ganglionic blocking medicines combined with enalapril, as in PHARMAPRESS CO, should only be administered under careful observation of the patient.

Concomitant use of other antihypertensive medicines may increase the hypotensive effects of PHARMAPRESS CO. Concomitant use with nitro-glycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

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

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

*Fluoroquinolones*

Concomitant use of fluoroquinolones and PHARMAPRESS CO may precipitate AKI (see sections 4.3 and 4.4). It has been reported that AKI occurred soon after ciprofloxacin was prescribed in patients taking enalapril, as in PHARMAPRESS CO. The interaction between ACE inhibitors and fluoroquinolones to precipitate AKI is a class effect for all ACE inhibitors and not just enalapril and also a class effect of all fluoroquinolones not just with ciprofloxacin.

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 or potassium supplements*

The potassium losing effect of thiazide diuretics, such as hydrochlorothiazide, as in PHARMAPRESS CO, is normally diminished by the effect of enalapril, as in PHARMAPRESS CO.

The use of potassium sparing medicines (including potassium-sparing diuretics e.g. spironolactone, eplerenone, triamterene or amiloride), potassium-containing salt substitutes or potassium supplements, or those patients taking other medicines associated with increases in serum potassium (e.g. heparin) may lead to a significant increase in serum potassium, particularly in patients with impaired renal function (see section 4.3).

*Lithium*

Lithium should generally not be given with diuretics. The renal clearance of lithium is reduced by diuretic medicines, such as hydrochlorothiazide and ACE-inhibitors, such as enalapril, as in PHARMAPRESS CO, and therefore there is a high risk of lithium toxicity. Reversible increases in serum lithium concentrations and toxicity have been reported

during concomitant administration of lithium with ACE inhibitors such as enalapril, and hydrochlorothiazide, as in PHARMAPRESS CO. The use of PHARMAPRESS CO and lithium is contraindicated (see section 4.3 and 4.4).

*Allopurinol*

The concurrent use of ACE inhibitors, such as enalapril, as in PHARMAPRESS CO, and allopurinol might increase the risk of neutropenia/agranulocytosis and serious infection especially in renal impairment (section 4.3 and 4.4).

*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 enalapril, as in PHARMAPRESS CO (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic or by increasing volume or salt intake.

*Kaliuretic diuretics (e.g. furosemide), carbenoxolone, or laxative abuse*

Hydrochlorothiazide, as in PHARMAPRESS CO, may increase the loss of potassium and/or magnesium.

*Tricyclic antidepressants, antipsychotics or anaesthetics*

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE inhibitors, such as enalapril, as in PHARMAPRESS CO, may result in further reduction of blood pressure (see sections 4.3 and 4.4).

*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 CO.

*Mammalian target of rapamycin (mTOR) inhibitors*

Patients taking concomitant mTOR inhibitor (e.g. temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see section 4.3 and 4.4).

*Neprilysin inhibitors*

Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy (e.g. sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.4). The concomitant use of enalapril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of enalapril therapy. Enalapril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

*Non-depolarising muscle relaxants*

The responsiveness to tubocurarine may be increased by the administration of thiazides, including hydrochlorothiazide, as in PHARMAPRESS CO.

*Barbiturates, alcohol or opioid analgesics*

Potentiation of orthostatic hypotension may occur with barbiturates, alcohol or opioid analgesics.

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

*Anti-diabetic medicine (insulin and oral medicines)*

Concomitant administration of ACE inhibitors, such as enalapril, as in PHARMAPRESS

CO, and antidiabetic medicines (insulins, oral hypoglycaemic medicines) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see section 4.3 and 4.4).

The dosage of the anti-diabetic medicine (insulin and oral medicines) may be required to be adjusted.

*Acetylsalicylic acid (e.g. aspirin), thrombolytics and β-blockers*

Enalapril, as in PHARMAPRESS CO, can be safely administered concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics and β-blockers.

*Cholestyramine and colestipol resins (anionic exchange resins)*

Absorption of hydrochlorothiazide, as in PHARMAPRESS CO, is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide, as in PHARMAPRESS CO, and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

*Increasing the QT Interval (e.g., quinidine, procainamide, amiodarone, sotalol)*

An increased risk of torsades de pointes exists with concomitant administration.

*Digitalis glycosides (e.g. digoxin)*

Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

*ACTH and corticosteroids*

ACTH and corticosteroids may intensify the depletion of electrolytes, particularly

potassium resulting in hypokalaemia.

*Non-steroidal anti-inflammatory drugs (NSAIDs)*

The diuretic, anti-hypertensive and natriuretic effects of diuretics can be reduced by the administration of NSAIDs including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) in some patients.

Therefore, the antihypertensive effect of ARBs, ACE inhibitors or diuretics may be attenuated by NSAIDs including selective COX-2 inhibitors. The co-administration of NSAIDs (including COX-2 inhibitors) and ARBs or ACE inhibitors 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.

*Pressor amines or sympathomimetics e.g. epinephrine (adrenalin) or norepinephrine (noradrenaline)*

A possible decreased response to pressor amines (e.g. adrenalin/noradrenaline) occur but not sufficient to preclude their use. Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors, such as enalapril, as in PHARMAPRESS CO.

*Cytostatics (e.g. cyclophosphamide, methotrexate)*

Hydrochlorothiazide, as in PHARMAPRESS CO, may reduce the renal excretion of cytotoxic medicines and potentiate their myelosuppressive effects.

**4.6 Fertility, pregnancy and lactation**

PHARMAPRESS CO is contraindicated in pregnancy and lactation, and also in patients

intending to become pregnant.

Pregnant women should be informed of the potential hazards to the foetus and must not take PHARMAPRESS CO 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 CO should be stopped immediately and if appropriate, alternative therapy should be started.

**Pregnancy**

**Enalapril maleate**

PHARMAPRESS CO passes through the placenta and can cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in new-borns and neonatal toxicity (renal failure, hypotension, and hyperkalaemia) have been reported after administration of PHARMAPRESS CO in the second and third trimester.

Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur. In addition, use of PHARMAPRESS CO during the first trimester of pregnancy has been associated with an increased risk of birth defects, in particular of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and the central nervous system (microcephaly, spina bifida) and of kidney malformations.

Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development.

Should exposure to PHARMAPRESS CO have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended (see section 4.3 and 4.4).
When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

**Hydrochlorothiazide**

Thiazides, including hydrochlorothiazide, as in PHARMAPRESS CO, cross the placental barrier and appear in cord blood. Hazards include foetal and neonatal jaundice and thrombocytopenia.

There is limited experience with hydrochlorothiazide, as in PHARMAPRESS CO, during pregnancy, especially during the first trimester. Based on the pharmacological mechanism of action of hydrochlorothiazide, as in PHARMAPRESS CO, its use during the second and third trimester may compromise foetal-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

PHARMAPRESS CO should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

PHARMAPRESS CO should not be used for essential hypertension in pregnant woman (see section 4.3). Infants whose mothers have taken PHARMAPRESS CO should be closely observed for hypotension, oliguria and hyperkalaemia. There is no experience with the removal of the combination medicine, PHARMAPRESS CO from the neonatal circulation. Enalapril, as in PHARMAPRESS CO, 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, as in PHARMAPRESS CO, which also crosses the placenta, from the neonatal circulation.

**Lactation**

Both enalapril and thiazides, including hydrochlorothiazide, as in PHARMAPRESS CO, appear in human milk. Mothers breastfeeding their infants should not be treated with PHARMAPRESS CO (see section 4.3). If use of PHARMAPRESS CO is deemed essential, the patient should stop breastfeeding. Hydrochlorothiazide, as in PHARMAPRESS CO, in high doses causing intense diuresis can inhibit the milk production.

**Fertility**

There is no fertility data.

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

a) *Tabulated list of adverse reactions*

*Enalapril maleate and hydrochlorothiazide combination, as in PHARMAPRESS CO.*

| System organ class | Frequent | Less frequent | Frequency unknown (cannot be estimated from the available data) |
|---|---|---|---|
| **Neoplasm benign, malignant and unspecified (including cysts and polyps)** | | | Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) |
| **Blood and the lymphatic system disorders** | | Decreases in haemoglobin, decreases in haematocrit, decrease in platelets, decrease in white cell count, anaemia (including aplastic and haemolytic), neutropenia, thrombocytopenia, agranulocytosis, bone marrow depression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases | |
| **Immune system disorders** | | Hypersensitivity/angioedema (angioedema of the face, extremities, lips, tongue, glottis and/or larynx) | |
| **Endocrine disorders** | | | Syndrome of inappropriate antidiuretic hormone secretion (SIADH) |
| **Metabolism and nutrition disorders** | Hypokalaemia, increase of cholesterol, increase of triglycerides, hyperuricaemia | Hyperglycaemia, hypoglycaemia, gout, hyponatraemia | |
| **Nervous system disorders** | Dizziness, insomnia, paraesthesia, headache, decreased libido, depression, syncope, taste alteration | Nervousness, somnolence, vertigo, paresis (due to hypokalaemia), confusion, insomnia, paraesthesia, decreased libido, dream abnormality, sleep disorders | |
| **Eye disorders** | Blurred vision | | Choroidal effusion |

| | | | |
|---|---|---|---|
| **Ear and labyrinth disorders** | | Tinnitus | |
| **Cardiac disorders** | Chest pain, palpitations, tachycardia, rhythm disturbances, angina pectoris | Flushing, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients. | Raynaud's phenomenon |
| **Vascular disorders** | Hypotension, orthostatic hypotension | | |
| **Respiratory, thoracic and mediastinal disorders** | Cough | Dyspnoea, rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma, pulmonary infiltrates, respiratory distress (including pneumonitis and pulmonary oedema), rhinitis, allergic alveolitis/eosinophilic pneumonia | |
| **Gastrointestinal disorders** | Nausea, diarrhoea abdominal pain | Dyspepsia, constipation, vomiting, flatulence, dry mouth, pancreatitis, ileus, anorexia, gastric irritations, dry mouth, peptic ulcer, stomatitis /aphthous ulcerations, glossitis, intestinal angioedema | |
| **Hepato-biliary disorders** | | Hepatic failure, hepatic necrosis (may be fatal), hepatitis – either hepatocellular or cholestatic, jaundice cholecystitis (in particular in patients with pre-existing cholelithiasis) | |
| **Skin and subcutaneous tissue disorders** | Rash (exanthema) | Diaphoresis, pruritus, erythema multiforme, Stevens-Johnson | Symptom complex which may include some or all of the following: |

| | | | |
|---|---|---|---|
| | | syndrome, exfoliative dermatitis, toxic epidermal necrolysis, purpura, cutaneous lupus erythematosus, erythroderma, pemphigus urticaria, alopecia | fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive antinuclear antibody, elevated erythrocyte sedimentation rate, eosinophilia, leukocytosis. Photosensitivity or other dermatologic manifestations may occur (DRESS syndrome) |
| **Musculoskeletal and connective tissue disorders** | Muscle cramps | | |
| **Renal and urinary disorders** | | Renal dysfunction, renal failure, proteinuria, oliguria, interstitial nephritis | |
| **Reproductive system and breast disorders** | | Impotence, gynaecomastia | |
| **General disorders and administrative site conditions** | Fatigue, asthenia | Malaise, fever | |
| **Investigations** | | Increases in blood urea, creatinine, elevations of liver enzymes, elevations of serum bilirubin | |

*Enalapril maleate as in PHARMAPRESS CO*

| **System organ class** | **Frequent** | **Less frequent** | **Frequency unknown** (cannot be estimated from the available data) |
|---|---|---|---|
| **Blood and the lymphatic system disorders** | | Anaemia (including aplastic and haemolytic) neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia , agranulocytosis, myelosuppression , pancytopenia, lymphadenopathy | |
| **Immune system disorders** | Hypersensitivity /angioedema of the face, extremities, lips, | Autoimmune diseases, intestinal angioedema | |

| | | | |
|---|---|---|---|
| | tongue, glottis and/or larynx | | |
| **Endocrine disorders** | | | Syndrome of inappropriate antidiuretic hormone secretion (SIADH) |
| **Metabolism and nutrition disorders** | | Hypoglycaemia, anorexia | |
| **Psychiatric disorders** | Depression | Confusion | |
| **Nervous system disorders** | Headache, dizziness, syncope | Somnolence, insomnia, nervousness, paraesthesia, vertigo, abnormal dreams, sleep disorders | |
| **Eye disorders** | Blurred vision | | |
| **Ear and labyrinth disorders** | | Tinnitus | |
| **Cardiac disorders** | Myocardial infarction, chest pain, cardiac rhythm disorders (dysrhythmia), angina pectoris, tachycardia | Palpitations | |
| **Vascular disorders** | Hypotension (including orthostatic hypotension), cerebrovascular accident (possibly secondary to excessive hypotension in risk patients) | 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/ eosinophilic pneumonia | |
| **Gastrointestinal disorders** | Nausea, diarrhoea, abdominal pain, taste alteration | Ileus, pancreatitis, vomiting, dyspepsia, constipation, gastric irritations, dry mouth, peptic/ aphthous ulcer, stomatitis, | |

| | | | |
|---|---|---|---|
| | | glossitis, flatulence | |
| **Hepato-biliary disorders** | | Hepatic failure, hepatitis (either hepatocellular or cholestatic), hepatitis including necrosis, cholestasis (including jaundice) | |
| **Skin and subcutaneous tissue disorders** | Rash | Diaphoresis, pruritus, urticaria, alopecia, erythema multiforme, Stevens-Johnson syndrome (SJS), exfoliative dermatitis, toxic epidermal necrolysis (TEN), pemphigus | A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, positive anti-nuclear antibody, elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis. Rash or other dermatological manifestations or photosensitivity may occur. |
| **Musculoskeletal and connective tissue disorders** | Asthenia | Muscle cramps | Gout and arthralgia |
| **Renal and urinary disorders** | | Renal dysfunction, renal failure, proteinuria, oliguria | |
| **Reproductive system and breast disorders** | | Impotence, gynaecomastia | |
| **General disorders and administrative site conditions** | Fatigue | Fever, malaise | |
| **Investigations** | Hyperkalaemia, increases in serum creatinine | Increases in blood urea content, hyponatraemia, elevations of liver enzymes, elevations of serum bilirubin | |

*Hydrochlorothiazide as in PHARMAPRESS CO*

| **System organ class** | **Frequent** | **Less frequent** | **Frequency unknown** (cannot be estimated from the available data) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Infections and infestations** | | | Sialadenitis |
| **Neoplasm benign, malignant and unspecified (including cysts and polyps)** | | | Non-melanoma skin cancer (Basal cell carcinoma and squamous cell carcinoma) |
| **Blood and the lymphatic system disorders** | | Agranulocytosis, thrombocytopenia | Leukopenia, neutropenia, aplastic anaemia, haemolytic anaemia, bone marrow depression |
| **Immune system disorders** | | | Anaphylactic reaction |
| **Metabolism and nutrition disorders** | Electrolyte imbalance (including hyponatraemia and hypokalaemia) | Anorexia | Hyperglycaemia, hyperuricaemia |
| **Nervous system disorders** | | | Restlessness |
| **Eye disorders** | | | Xanthopsia, transient blurred vision, choroidal effusion |
| **Vascular disorders** | | | Necrotising angiitis (vasculitis) |
| **Respiratory, thoracic and mediastinal disorders** | | | Respiratory distress (including pneumonitis and pulmonary oedema) |
| **Gastrointestinal disorders** | | Pancreatitis, gastric irritation | |
| **Hepato-biliary disorders** | | | Jaundice (intrahepatic cholestatic jaundice) |
| **Skin and subcutaneous tissue disorders** | | Photosensitivity, urticaria | Toxic epidermal necrolysis (TEN), purpura |
| **Musculoskeletal and connective tissue disorders** | | Gout and arthralgia | Muscle spasm |
| **Renal and urinary disorders** | | Interstitial nephritis, glycosuria | |
| **General disorders and administrative site conditions** | | Fever | |

b) *Description of selected adverse reactions*:

*Eye disorders*: Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

*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 Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

**Aspen Pharmacare:**

**E-mail:** Drugsafety@aspenpharma.com

**Tel:** 0800 118 088

**4.9 Overdose**

**Treatment**

On the treatment of overdosage with PHARMAPRESS CO, no specific information is available. Treatment is symptomatic and supportive.

Therapy with PHARMAPRESS CO should be discontinued and the patient observed closely. Suggestive measures include induction of emesis, administration of activated charcoal, administration of a laxative if the ingestion is recent, and correction of electrolyte imbalance, hypotension and dehydration, by established procedures introduced within 2 hours after ingestion.

**Enalapril maleate as in PHARMAPRESS CO**

**Symptoms**

Hypotension is the most prominent feature of overdosage, 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 CO, may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

**Treatment**

The recommended treatment of overdosage is intravenous infusion of normal 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, as in PHARMAPRESS CO (e.g. emesis, gastric lavage, administration of absorbents, and sodium sulphate). Haemodialysis may be used to remove enalapril, as in PHARMAPRESS CO from the general circulation.

Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

**Hydrochlorothiazide as in PHARMAPRESS CO**

**Symptoms**

The most common signs and symptoms observed are those caused by electrolyte depletion (hypochloraemia, hypokalaemia, hyponatraemia) and from excessive diuresis, dehydration will result.

Cardiac dysrhythmias may be accentuated by hypokalaemia, if digoxin has also been administered.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Category and class: 7.1.3 Other hypotensives

Pharmacotherapeutic group: Vascular medicines

ATC code: C09BA02.

*Mechanism of action*

Enalapril maleate is an angiotensin-converting enzyme inhibitor (ACE inhibitor).

Hydrochlorothiazide is a diuretic with antihypertensive properties.

### 5.2 Pharmacokinetic properties

**Enalapril maleate**

**Absorption**

Enalapril acts as a pro-medicine of the diacid enalaprilat, its active form, which is poorly absorbed orally. About 60 % of an oral dose of enalapril is absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 1 hour.
The absorption of oral enalapril maleate is not influenced by the presence of food in the gastrointestinal tract.

**Distribution**

Steady state serum concentrations of enalaprilat are achieved by the fourth day of administration of enalapril maleate in patients with normal renal function.

**Metabolism**

Enalapril is extensively hydrolysed in the liver to the active metabolite enalaprilat; peak plasma concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril.

**Elimination**

After an oral dose, enalapril is excreted in the urine and in faeces, as enalaprilat and unchanged enalapril, with the urinary route predominating. The elimination of enalaprilat is multiphasic but the effective half-life for accumulation after multiple doses of enalapril is reported to be about 11 hours in patients with normal renal function.

**Hydrochlorothiazide**

Hydrochlorothiazide is absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 % to 70 %.

**Distribution**

Hydrochlorothiazide appears to be preferentially bound to red blood cells.

**Metabolism**

Hydrochlorothiazide is excreted unchanged.

**Elimination**

Hydrochlorothiazide has been estimated to have a plasma half-life of between about 5 and 15 hours. Hydrochlorothiazide is eliminated rapidly by the kidney with at least 61 % of the oral dose eliminated unchanged within 24 hours in the urine.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate, maize starch, 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 light.

Store in a dry place.

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 matt silver polyamide, aluminium and polyvinylchloride film sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton.

**6.6 Special precautions for disposal**

No special requirements

**7. HOLDER OF THE CERTIFICATE OF REGISTRATION**

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

## 8. REGISTRATION NUMBER

34/7.1.3/0190

## 9. DATE OF FIRST AUTHORISATION

20 April 2001

## 10. DATE OF REVISION OF TEXT

03 June 2024

| |
|---|
| Namibia: NS2 04/7.1.3/0120 |

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