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SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ENAP-CO 20,0/12,5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ENAP-CO tablet contains 20 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide.

Each tablet contains sugar (lactose monohydrate 122.16 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Round, flat, white, one-side scored tablet, with bevel edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENAP-CO is indicated for the treatment of hypertension in patients stabilised on the individual components administered at the same dosages.

4.2 Posology and method of administration

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Hypertension:

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

Special populations

Dosage in Renal Insufficiency:

Do not use ENAP-CO as initial therapy in any patient with renal insufficiency (see section 4.3).

In patients with renal impairment, thiazides (including hydrochlorothiazide as in ENAP-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).

ENAP-CO may however be used in patients with creatinine clearance greater than 30 mL/minutes and less than 80 mL/minutes, but only after the individual components have been successfully titrated.

Paediatric population

No data are available.

Method of administration

For oral use.

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Missed dose

Doctors should advise patients who forget to take ENAP-CO to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- Hypersensitivity to enalapril maleate, hydrochlorothiazide, other sulphonamide-derived medicines or to any of the ingredients of ENAP-CO (see section 6.1).
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): Such patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min) or anuria.
- Bilateral renal artery stenosis.
- Patients with severe hepatic impairment.
- Renal artery stenosis in patients with a single kidney or aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as eplerenone, spironolactone, triamterene and amiloride (see section 4.5).
- Patients with Addison’s disease.
- Lithium therapy: Concomitant administration with ENAP-CO may lead to toxic blood concentrations of lithium (see section 4.5).
- The concomitant use of ENAP-CO with aliskiren-containing products in patients with

diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) is contraindicated (see sections 4.4 and 4.5).

- Concomitant use of fluoroquinolone with ACE inhibitors, such as ENAP-CO is contraindicated in patients with moderate renal impairment (Creatine Clearance ≤ 30 mL/min) and in elderly patients.
- Combination with sacubitril/valsartan due to the increased risk of angioedema. Do not administer ENAP-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).
- Porphyria.

4.4 Special warnings and precautions for use

Safety in pregnancy and lactation has not been established. Should a woman become pregnant while receiving ENAP-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, including ENAP-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.

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Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with enalapril maleate, as contained in ENAP-CO. This may occur at any time during treatment. In such cases, ENAP-CO should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. The condition may resolve without treatment 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.

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, which may include subcutaneous epinephrine solution 1:1000 (0,3 mL to 0,5 mL) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ENAP-CO have been reported to have a higher incidence of angioedema compared to non-black patients. However, it appears that black patients have an increased risk of angioedema in general.

A history of angioedema unrelated to ACE-inhibitor therapy may expose patients to an increased risk of developing angioedema while receiving ENAP-CO (see section 4.3).

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Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Hypersensitivity:

Therapy with ENAP-CO may cause sensitivity reactions in certain patients, with or without a history of allergy or bronchial asthma. Reports of exacerbation or activation of systemic lupus erythematosus have been associated with the use of ENAP-CO.

Anaphylactoid reactions:

Rarely, patients receiving ENAP-CO during desensitisation with hymenoptera venom or during low density lipoprotein (LDL)-apheresis with dextran sulphate, have experienced life-threatening anaphylactoid reactions. These reactions may be avoided by temporarily withholding ENAP-CO prior to each desensitisation/apheresis.

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ENAP-CO and aliskiren is therefore contraindicated (see section 4.3). ENAP-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.

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Hypotension and electrolyte fluid imbalance:

After administration of the initial dose of ENAP-CO, symptomatic hypotension may occur. Hypotension is more likely in patients who are volume depleted, e.g. by diarrhoea or vomiting, diuretic therapy or dietary salt restriction.

Discontinue diuretic therapy for 2-3 days before therapy with ENAP-CO is initiated. In patients with ischaemic heart or cerebrovascular disease, therapy should be administered with extreme caution because an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

Such patients should be monitored for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur during inter-current diarrhoea or vomiting, dietary salt restriction or due to diuretic therapy including hydrochlorothiazide (as in ENAP-CO). Serum electrolytes should be periodically determined at appropriate intervals when treating these patients.

ENAP-CO can cause electrolyte or fluid imbalance (e.g. hypochloraemic alkalosis, hypokalaemia and hyponatraemia). 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.

Although hypokalaemia may develop during treatment with hydrochlorothiazide's, concurrent therapy with enalapril, as contained in ENAP-CO, may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver,

patients experiencing brisk diuresis, 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 contained in ENAP-CO, may increase the urinary excretion of magnesium, which may result in hypomagnesemia.

In hypertensive patients with 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, ENAP-CO therapy should be started under medical supervision and the patients should be followed closely whenever the dose of ENAP-CO 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.

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 solitary kidney are treated with ENAP-CO and loss of renal function may occur with only mild changes in serum creatinine (see section 4.3).

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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 ENAP-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 ENAP-CO may be necessary.

Aortic stenosis/hypertrophic cardiomyopathy:

ENAP-CO should not be given to 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:

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

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Increases in blood urea and serum creatinine have developed in some hypertensive patients with no apparent pre-existing renal disease when enalapril maleate has been given concomitantly with a diuretic. Should this occur during therapy with ENAP-CO, the combination should be discontinued.

Renal failure has been associated with ENAP-CO mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis (see section 4.3). ENAP-CO associated renal failure is usually reversible if recognised promptly and treated appropriately.

ENAP-CO may not be appropriate for use in patients with renal impairment.
Hydrochlorothiazides are ineffective at creatinine clearance values of 30 mL/min or below (i.e. moderate or severe renal insufficiency) (see section 4.3).
ENAP-CO should not be administered to patients with renal insufficiency (creatinine clearance ≤ 80 mL/min) until titration of the individual components has shown the need for the doses present in ENAP-CO.

The use of ENAP-CO is not indicated in patients requiring dialysis for renal failure (see section 4.2).
Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g. AN69®) receiving concomitant ENAP-CO treatment. A different type of dialysis membrane or a different class of antihypertensive medicine, should be considered when treating such patients.

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Since there is no experience of therapy with enalapril maleate in patients with recent kidney transplantation, treatment with ENAP-CO in this patient group is not recommended.

Concomitant use of fluoroquinolones and ACE inhibitors, such as ENAP-CO, may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients. (See section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment, with fluoroquinolones or ACE inhibitors, such as ENAP-CO, whether used separately and/or concomitantly.

Hyperkalaemia:

The possibility of hyperkalaemia occurrence cannot be excluded with the combination of enalapril maleate and a low dose of hydrochlorothiazide, as contained in ENAP-CO. ENAP-CO increases serum potassium. Risk factors which may lead to the development of hyperkalaemia include those patients 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.

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Concomitant treatment of ENAP-CO and any of the above mentioned medicines is therefore contraindicated (see section 4.3).

Hepatic disease:

Minor alterations of fluid and electrolyte balance may precipitate hepatic encephalopathy and coma, therefore, ENAP-CO should be used with caution in patients with impaired hepatic function or progressive liver disease.

Rarely, ENAP-CO has 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 ENAP-CO who develop jaundice or marked elevations of hepatic enzymes should discontinue treatment with ENAP- CO and receive appropriate medical follow-up.

Surgery/anaesthesia:

ENAP-CO is known to block angiotensin II formation secondary to compensatory renin release in patients undergoing major surgery or during anaesthesia with medicines that produce hypotension. Should hypotension occur and be considered to be due to this mechanism, volume expansion can be used to correct the fall in blood pressure.

Metabolic and endocrine effects:

Adjustment to the dosage of antidiabetic medicines, including insulin, may be required since ENAP-CO may impair glucose tolerance.

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Diabetic patients treated with insulin or oral diabetic medicines should be closely monitored for hypoglycaemia, especially during the first month of combined used with ENAP-CO.

ENAP-CO may also decrease levels of serum magnesium, potassium and sodium.

In some cases, ENAP-CO may be associated with increases in cholesterol and triglyceride levels.However, at the 12,5 mg dose of hydrochlorothiazide, minimal or no effect has been documented.

In the absence of known disorders of calcium metabolism, ENAP-CO may cause an intermittent elevation of serum calcium and decrease urinary calcium excretion. Marked hypercalcaemia may be evidence of latent hyperparathyroidism. ENAP-CO should be discontinued before parathyroid function is tested.

A dose-related effect of hydrochlorothiazide may cause hyperuricaemia and/or gout in some patients. Enalapril maleate, as in ENAP-CO, may increase urinary uric acid, therefore further increasing the hyperuricaemic effect of hydrochlorothiazide. Determination of serum electrolytes should be performed at regular intervals.

Cough:

Cough has been reported with the use of ENAP-CO. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ENAP-CO-induced cough should be considered as part of the differential diagnosis of cough.

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Neutropenia, agranulocytosis:

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ENAP-CO.

In patients with normal renal function and no other complicating factors, neutropenia occurs infrequently.

ENAP-CO should be used with extreme caution in patients with collagen vascular disease, immunosuppressant treatment, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if pre-existing impaired renal function is present. Some patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If ENAP-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:

ENAP-CO is less effective in lowering blood pressure in black patients than in non-black patients, possibly due to 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) exposure has been observed in two epidemiological studies. Photosensitising actions of HCTZ could act as a possible mechanism for NMSC.

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Patients taking ENAP-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 in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. ENAP-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 and 4.8).

Lithium:

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

Anti-doping test:

Hydrochlorothiazide 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, 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.

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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.

Information on excipients of ENAP-CO:

ENAP-CO contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ENAP-CO.
ENAP-CO contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Elderly Use:

No significant differences in efficacy and tolerability were identified in elderly or younger hypertensive patients when enalapril maleate and hydrochlorothiazide were administered concomitantly.

Paediatric population

The safety and efficacy of ENAP-CO in children have not been established.

4.5 Interaction with other medicines and other forms of interaction

Other antihypertensive therapy:

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When other antihypertensive medicines are taken concomitantly with ENAP-CO the hypotensive effects of enalapril maleate and hydrochlorothiazide may be increased. Blood pressure may be further reduced if ENAP-CO is combined with nitroglycerine and other nitrates, or other vasodilators.

The combination of ENAP-CO with ganglionic blocking or adrenergic blocking medicines, should only be considered if the patient can be kept under careful observation.

Lithium:

The combination of lithium and diuretics should be avoided. Renal clearance of lithium is reduced by diuretic medicines and ACE-inhibitors, exposing patients to a high risk of lithium toxicity (see section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 (COX-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. Therefore, the antihypertensive effect of ENAP-CO may be attenuated by NSAIDs including selective COX-2 inhibitors.

The co-administration of NSAIDs (including COX-2 inhibitors) and ENAP-CO exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, 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.

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

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see sections 4.3 and 4.4).

Angiotensin converting enzyme (ACE) inhibitors:

Concomitant use of fluoroquinolones and ACE inhibitors such as ENAP-CO may precipitate acute kidney injury (AKI). Reports indicate that AKI occurred soon after ciprofloxacin was prescribed in patients taking enalapril. 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 the medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Enalapril maleate:

Serum Potassium:

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

Hyperkalaemia may develop in the presence of risk factors such as renal insufficiency, diabetes mellitus and concomitant use of potassium-sparing diuretics (e.g. eplerenone,

spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes (see section 4.3).

Diuretics (hydrochlorothiazide or loop diuretics):

When starting therapy with enalapril (as in ENAP-CO), prior treatment with high dose diuretics may lead to a risk of hypotension and volume depletion. Discontinuation of ENAP-CO, or increasing volume of salt intake, will reduce these hypotensive effects.

Tricyclic antidepressants/antipsychotics/anaesthetics:

Taking certain anaesthetics, antipsychotics or tricyclic antidepressants concurrently with enalapril (as in ENAP-CO) may further reduce blood pressure (see sections 4.3. and 4.4).

Sympathomimetics:

The antihypertensive effect of ENAP-CO may be reduced by sympathomimetics.

Gold:

In patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy with ENAP-CO, nitritoid reactions (with symptoms including facial flushing, nausea, vomiting and hypertension) have been reported.

Alcohol:

The hypotensive effect of enalapril maleate, as in ENAP-CO, is enhanced by alcohol.

Antidiabetics (oral medicines and insulin):

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An increased blood-glucose lowering effect with risk of hypoglycaemia may be caused by concurrent administration of ACE inhibitors, including enalapril (as in ENAP-CO), and antidiabetic medicines (oral hypoglycaemic medicines, insulins). This increase appears more likely to occur during the first weeks of combined treatment, and in patients with impaired renal function.

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

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

Allopurinol:

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

Other medicines that may increase the risk of angioedema:

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).

Co-trimoxazole (trimethoprim/sulfamethoxazole):

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for

hyperkalaemia (see section 4.4).

Hydrochlorothiazide:

Non-depolarising muscle relaxants:

Responsiveness to tubocurarine may be increased during ENAP-CO.

Antidiabetic medicines (oral medicines and insulin):

The dosage of the antidiabetic medicine (insulin and oral medicines) may have to be adjusted.

Treatment with a thiazide may influence glucose tolerance. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Alcohol, barbiturates or narcotics:

Hydrochlorothiazide (as in ENAP-CO) may potentiate orthostatic hypotension.

Cholestyramine and colestipol resins:

The presence of anionic exchange-resins impairs the absorption of hydrochlorothiazide, as contained in ENAP-CO. Cholestyramine and colestipol resins, in single doses, bind the hydrochlorothiazide and reduce its absorption from the gastro-intestinal tract by up to 85 % and 43 %, respectively.

Increasing of the QT interval (e.g. quinidine, procainamide, amiodarone, sotalol):

Increased risk of torsades de pointes.

Digoxin:

The response of the heart to the toxic effects of digoxin (e.g. increased ventricular irritability) can be sensitized or exaggerated by hypokalaemia.

Corticosteroids, ACTH:

Increased electrolyte depletion, particularly hypokalaemia, may occur.

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

The loss of magnesium and/or potassium may be increased by hydrochlorothiazide (as in ENAP-CO).

Pressor Amines - Epinephrine (adrenaline):

A decreased response to pressor amines may occur, but this is generally not sufficient to preclude their use.

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Cytostatics (e.g. cyclophosphamide, methotrexate):

The renal excretion of cytotoxic medicines may be reduced and their myelosuppressive effects increased by hydrochlorothiazide (as in ENAP-CO).

Medicines used to treat gout (probenecid, sulfinpyrazone and allopurinol):

A dose adjustment of uricosuric agents may be necessary, as hydrochlorothiazide may increase the level of serum uric acid. An increase in the dose of probenecid or sulfinpyrazone may be necessary. Co-administration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. Atropine, biperiden):

Increase the bioavailability of thiazide diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Salicylates:

Hydrochlorothiazide may enhance the toxic effect of high dose salicylates on the central nervous system.

Methyldopa:

Isolated cases of haemolytic anaemia occurring during concomitant use of hydrochlorothiazide and methyldopa have been reported.

Cyclosporin:

Concomitant treatment with cyclosporin may increase the risk of hyperuricaemia and gout-type complications.

Carbamazepine:

Risk of symptomatic hyponatraemia. Clinical and laboratory monitoring is required.

Iodinated contrast media:

In case of dehydration caused by diuretics, the risk of acute renal failure is increased, especially when using large doses of iodinated contrast media.

Patients should be rehydrated before use.

4.6 Fertility, pregnancy and lactation

Enalapril maleate

Pregnancy

The use of ENAP-CO is contraindicated during pregnancy.

Pregnant women should be informed of the potential hazards to the foetus and must not take ENAP-CO during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ENAP-CO should be stopped immediately and if appropriate,

alternative therapy should be started.

Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or

ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spina bifida) and of kidney malformations.

ENAP-CO passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

Oligohydramnios, as well as hypotension, oliguria and anuria in new-borns have been reported after administration of ENAP-CO during the second and third trimester and may result in limb contractures, craniofacial deformations and hypoplastic lung development. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Should exposure to enalapril have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended (see section 4.3 and 4.4).

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental barrier and appears in cord blood. Hazards include foetal and neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occur in the adult.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Based on the pharmacological mechanism of action of hydrochlorothiazide, 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.

In 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, ENAP-CO should not be administered.

ENAP-CO should not be used for essential hypertension in pregnant woman (see section 4.3).

Infants whose mothers have taken ENAP-CO should be closely observed for hypotension, oliguria and hyperkalaemia. There is no experience with the removal of the combination product, ENAP-CO, from the neonatal circulation.
Enalapril, which crosses the placenta, has been removed from
the neonatal circulation by peritoneal dialysis with some clinical benefit.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

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ENAP-CO has moderate influence on the ability to drive and use machines.

When driving vehicles or operating machinery it should be taken into account that dizziness, drowsiness and blurred vision may occur whilst taking ENAP-CO.

Patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ENAP-CO does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Tabulated summary of adverse reactions

Hydrochlorothiazide + enalapril maleate combination:

System Organ Class	Frequency	Side effects
Neoplasms benign and malignant (including cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders	Less frequent	Decreases in haemoglobin, decreases in haematocrit, decrease in platelets and white cell count, anaemia (including aplastic and haemolytic), neutropenia, thrombocytopenia, agranulocytosis, bone marrow depression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases

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Immune system disorders	Less frequent	Hypersensitivity/angioedema (Angioedema of the face, extremities, lips, tongue, glottis and/or larynx)
Endocrine disorders	Frequency unknown	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Frequent Less frequent	Hypokalaemia, cholesterol increase, triglycerides increase Hyperglycaemia, hyperuricaemia, gout, hypoglycaemia, hyponatraemia
Psychiatric disorders	Less frequent	Decreased libido
Nervous system disorders	Frequent Less frequent	Dizziness, insomnia, paraesthesia, headache, depression, syncope, taste alteration Nervousness, somnolence, vertigo, paresis due to hypokalaemia, confusion, dream abnormality, sleep disorders
Eye disorders	Frequent Frequency unknown	Blurred vision Choroidal effusion
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent Less frequent Frequency unknown	Chest pain, palpitations, tachycardia, rhythm disturbances, angina pectoris Flushing, myocardial infarction, cerebrovascular accident, possibly due to non-orthostatic hypotension in high risk patients Raynaud's phenomenon

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Vascular disorders	Frequent	Orthostatic effects including hypotension
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	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	Frequent Less frequent	Nausea, diarrhoea, vomiting, abdominal pain Dry mouth, flatulence, dyspepsia, abdominal pain, constipation, pancreatitis, ileus, anorexia, gastric irritations, peptic ulcer, stomatitis/aphthous ulcerations, glossitis, intestinal angioedema
Hepatobiliary disorders	Less frequent	Hepatic failure, hepatic necrosis (may be fatal), hepatitis – either hepatocellular or cholestatic, jaundice, cholecystitis (in particular in patients with pre-existing cholelithiasis)

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Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Rash Diaphoresis, pruritus, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, toxic epidermal necrolysis, purpura, cutaneous lupus erythematosus, erythroderma, pemphigus urticaria, alopecia 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, elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis, photosensitivity or other dermatologic manifestations may occur (DRESS syndrome).
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Muscle cramps Arthralgia
Renal and urinary disorders	Less frequent	Renal dysfunction, renal failure, proteinuria, oliguria, interstitial nephritis
Reproductive system and breast disorders	Less frequent	Impotence, gynaecomastia
General disorders and administrative site conditions	Frequent Less frequent	Fatigue, asthenia Malaise, fever

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Investigations	Less frequent	Increases in blood urea, increases in serum creatinine, elevations of liver enzymes, elevations of serum bilirubin, hyperkalaemia

Enalapril maleate:

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Decreases in haemoglobin and haematocrit, neutropenia, thrombocytopenia, bone marrow depression, anaemia, agranulocytosis, myelosuppression, pancytopenia, lymphadenopathy
Immune system disorders	Frequent Less frequent	Hypersensitivity/angioedema, which may be fatal, of the face, extremities, lips, tongue, glottis and/or larynx Autoimmune diseases, intestinal angioedema
Endocrine disorders	Frequency unknown	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Less frequent	Anorexia, hypoglycaemia
Psychiatric disorders	Frequent Less frequent	Depression Confusion
Nervous system disorders	Frequent Less frequent	Headache Abnormal dreams, insomnia, nervousness, paraesthesia, somnolence, sleep disorders, vertigo

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Eye disorders	Frequent	Blurred vision
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent Less frequent	Myocardial infarction, cerebrovascular accident (secondary to excessive hypotension in high risk patients), chest pain, cardiac rhythm disturbances, angina pectoris, tachycardia Palpitations
Vascular disorders	Frequent Less frequent	Dizziness, hypotension (including orthostatic hypotension), syncope Orthostatic hypotension, Raynaud's phenomenon, flushing
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Cough, dyspnoea Bronchospasm/asthma, pulmonary infiltrates, rhinorrhoea, sore throat and hoarseness, rhinitis, allergic alveolitis/eosinophilic pneumonia
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain, diarrhoea, nausea, taste alteration Constipation, dyspepsia, glossitis, ileus, intestinal angioedema, pancreatitis, stomatitis, vomiting, dry mouth, peptic/ aphthous ulcer, flatulence
Hepatobiliary disorders	Less frequent	Hepatic failure, hepatitis - either hepatocellular or cholestatic, jaundice

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Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Rash Alopecia, diaphoresis, erythema multiforme, exfoliative dermatitis, pruritus, pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria Photosensitivity, a symptom complex, which may include fever, serositis, vasculitis, myalgia, myositis, arthralgia/arthritis, a positive anti-nuclear antibody, elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis, has been reported. Dermatologic manifestations, such as rash or photosensitivity may occur
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Asthenia Muscle cramps Gout, arthralgia
Renal and urinary disorders	Less frequent	Renal dysfunction, renal failure, oliguria, proteinuria
Reproductive system and breast disorders	Less frequent	Impotence, gynaecomastia
General disorders and administrative site conditions	Frequent	Fatigue
Investigations	Frequent Less frequent	Serum creatinine increases, hyperkalaemia Increases in blood urea, hyponatraemia, raised liver enzymes and/or serum bilirubin levels

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Hydrochlorothiazide:

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequency unknown	Sialadenitis
Neoplasms benign and malignant (including cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)
Blood and lymphatic system disorders	Less frequent Frequency unknown	Agranulocytosis, thrombocytopenia Neutropenia, aplastic anaemia, haemolytic anaemia, leukopenia, bone marrow depression
Immune system disorders	Frequency unknown	Anaphylactic reaction
Metabolism and nutrition disorders	Frequent Less frequent Frequency unknown	Electrolyte imbalance (including hyponatraemia and hypokalaemia) Anorexia Hyperglycaemia, hyperuricaemia
Nervous system disorders	Frequency unknown	Restlessness
Eye disorders	Frequent Frequency unknown	Transient blurred vision Xanthopsia, choroidal effusion
Vascular disorders	Frequency unknown	Hypotension, Necrotising angiitis (vasculitis)
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Respiratory distress (including pneumonitis and pulmonary oedema)

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Gastrointestinal disorders	Less frequent	Pancreatitis, gastric irritation
Hepatobiliary disorders	Frequency unknown	Glycosuria, jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Photosensitivity, urticaria Purpura, toxic epidermal necrolysis (TEN)
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Gout, arthralgia Muscle spasm
Renal and urinary disorders	Frequency unknown	Interstitial nephritis, glycosuria
General disorders and administrative site conditions	Less frequent	Fever

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

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4.9 Overdose

Signs and symptoms:

Enalapril Maleate:

Overdosage is primarily characterised by hypotension, which commences approximately six hours after ingestion of ENAP-CO, resulting from blockade of the renin-angiotensin system, and stupor.

Symptoms associated with an overdose of enalapril, include anxiety, bradycardia, circulatory shock, cough, dizziness, electrolyte disturbances, hyperventilation, palpitations, renal failure and tachycardia.

Hydrochlorothiazide:

Overdosage with ENAP-CO, is commonly associated with signs and symptoms caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. Hypokalaemia may accentuate cardiac dysrhythmias if digitalis has also been administered.

Management of overdose

Treatment is symptomatic and supportive. The following measures have been suggested: induction of emesis and/or correction of dehydration, electrolyte imbalance and hypotension using established procedures which should be introduced within 2 hours after ingestion. Haemodialysis can be used to remove enalaprilat from the general circulation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Pharmacotherapeutic group: Vascular medicines

ATC code: C09BA02

Pharmacological classification: A 7.1.3 Vascular medicines - Other Hypotensives

Mechanism of action

The combination tablet of an angiotensin-converting enzyme (ACE) inhibitor (enalapril maleate) and a diuretic (hydrochlorothiazide), which produces an additive antihypertensive effect. The active metabolite, enalaprilat, is formed by hydrolysation of enalapril maleate.

5.2 Pharmacokinetic properties

Enalapril maleate

Absorption:

When administered orally, enalapril maleate is rapidly absorbed, and peak serum concentrations are achieved within one hour. Approximately 60 % of an oral dose is absorbed from the gastrointestinal tract, as was shown by urinary recovery studies.

The absorption of oral enalapril maleate is not influenced by the presence of food in the gastro-intestinal tract. The extent of absorption and hydrolysis of enalapril maleate are similar for the various doses in the recommended therapeutic range.

Distribution:

Enalapril maleate crosses the placental barrier.

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

Biotransformation:

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Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril maleate.

Following absorption, oral enalapril maleate is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin-converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate. The principal components in urine are enalaprilat, accounting for about 40 % of the dose, and intact enalapril maleate. Except for conversion to enalaprilat, there is no evidence of significant metabolism of enalapril maleate. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE.

Elimination:

Excretion of enalapril maleate is primarily renal. The principal components in urine are enalaprilat, accounting for about 40 % of the dose, and intact enalapril maleate. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril maleate is 11 hours.

Renal impairment:

Enalaprilat may be removed from the general circulation by haemodialysis.

Hydrochlorothiazide

Absorption:

When administered orally, hydrochlorothiazide shows a bioavailability of 71 % ± 15 %. Hydrochlorothiazide crosses the placental, but not the blood-brain barrier.

Distribution:

When plasma levels of hydrochlorothiazide have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5,6 and 14,8 hours.

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Biotransformation:

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

Elimination:

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61 % of the oral dose is eliminated unchanged within 24 hours.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Maize starch

Pre-gelatinised starch

Sodium hydrogen carbonate

Talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

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6.4 Special precautions for storage

Store at or below 30 °c in a dry place.

Protect from light.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

Available in cold formed OPA/Al/PVC film and aluminium foil blisters of 30 tablets packed into a printed outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

A34/7.1.3/0088

9. DATE OF FIRST AUTHORISATION

Date of registration: 03 February 1999

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10. DATE OF REVISION OF THE TEXT

11 October 2024

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