PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Enalapril Co 20/12,5 Biotech Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg enalapril maleate and 12,5 mg hydrochlorothiazide as active ingredients.

Excipient(s) with known effect

Enalapril Co 20/12,5 Biotech contains sugar (lactose monohydrate) 130,10 mg per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Enalapril Co 20/12,5 Biotech are pale yellow colour, circular, biconvex uncoated tablets with breakline on one side & plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enalapril Co 20/12,5 Biotech 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 dosage is 1 tablet, administered once daily. If necessary, the dosage may be increased to a maximum of 2 tablets, administered once daily.

Special populations

Dosage in Renal insufficiency

Thiazides, including hydrochlorothiazide as contained in Enalapril Co 20/12,5 Biotech 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).

Enalapril Co 20/12,5 Biotech is not to be used as initial therapy in any patient with renal insufficiency.

In patients with renal clearance of > 30 and < 80 ml/min, Enalapril Co 20/12,5 Biotech may be used but only after titration of the individual components.

Paediatric population

Safety and effectiveness in children have not been established.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to enalapril, hydrochlorothiazide, other sulphonamide derived medicines or to any of the excipients of Enalapril Co 20/12,5 Biotech (see section 6.1).
- Severe renal impairment (creatinine clearance ≤ 30 ml/min).
- Anuria.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.

- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive, cardiomyopathy (HOCM).
- Pregnancy and lactation (see section 4.6).
- Severe hepatic impairment.
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant use of Enalapril Co 20/12,5 Biotech with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with Enalapril Co 20/12,5 Biotech may lead to toxic blood concentrations of lithium (see section 4.5).
- The concomitant use of Enalapril Co 20/12,5 Biotech with aliskiren-containing medicines is contraindicated (see section 4.4).
- Patients with Addison's disease
- Concomitant use 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 increased risk of angioedema. Do not administer Enalapril Co 20/12,5 Biotech 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 carcinoma and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving Enalapril Co 20/12,5 Biotech, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine. Should a woman contemplate pregnancy, the doctor should institute alternative medication (see section 4.6)

Hypotension and Electrolyte Fluid Imbalance

Symptomatic hypotension is seen in uncomplicated hypertensive patients. In hypertensive patients receiving Enalapril Co 20/12,5 Biotech, symptomatic hypotension may occur following the initial dose; this is more likely to occur if the patient has been volume depleted, e.g., by diuretic therapy, dietary salt restriction, diarrhoea or vomiting (see sections 4.5 and 4.8). Previous diuretic therapy should be discontinued for 2-3 days prior to initiation of treatment with Enalapril Co 20/12,5 Biotech. Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. Special attention should be paid to patients with ischemic heart or cerebrovascular disease in whom 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 observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of Enalapril Co 20/12,5 Biotech 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.

Thiazides (including hydrochlorothiazide) can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). 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 use of thiazide diuretics, concurrent therapy with enalapril 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.

Thiazides may have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contra-indication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Enalapril Co 20/12,5 Biotech. 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 Enalapril Co 20/12,5 Biotech, may be necessary.

Renal Function Impairment

Renal failure has been reported in association with enalapril and has been observed 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 is usually reversible.
Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic.
If this occurs, therapy with Enalapril Co 20/12,5 Biotech should be discontinued. This situation should raise the

possibility of underlying renal artery stenosis. Thiazides 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 section 4.2).

Enalapril Co 20/12,5 Biotech should not be administered to patients with renal insufficiency (creatinine clearance < 80 ml/min and > 30 ml/min) until titration of the individual components, enalapril and hydrochlorothiazide, have shown the need for the doses present in this combination formulation (see section 4.2).

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Lithium

The combination of lithium with enalapril and diuretic medicines is generally not recommended (see section 4.5).

Aortic Stenosis/Hypertrophic Cardiomyopathy

ACE inhibitors 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.

Renovascular Hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with Enalapril Co 20/12,5 Biotech. Loss of renal

function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

Haemodialysis Patients

The use of enalapril is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive medicine.

Kidney Transplantation

There is no experience regarding the administration of enalapril in patients with a recent kidney transplantation. Treatment with enalapril as contained in Enalapril Co 20/12,5 Biotech is therefore not recommended.

Hepatic failure

ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Enalapril Co 20/12,5 Biotech who develop jaundice or marked elevations of hepatic enzymes should discontinue the Enalapril Co 20/12,5 Biotech and receive appropriate medical follow-up.

Thiazides 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.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril as contained in Enalapril Co 20/12,5 Biotech should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these

complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril 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.

Hyperkalaemia

The combination of enalapril and a low-dose diuretic cannot exclude the possibility of a hyperkalaemia occurring. Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. 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 medicine associated with increases in serum potassium (e.g., heparin, trimethoprim-containing products such as cotrimoxazole).

The use of potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, or other medicine that may increase serum potassium, 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 and any of the above-mentioned medicines is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril maleate. This may occur at any time during treatment. In such cases, Enalapril Co 20/12,5 Biotech should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since

treatment with antihistamines and corticosteroids may not be sufficient.

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 adrenaline (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 of black ethnicity receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to white patient. 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 receiving an ACE inhibitor (see section 4.3).

Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema.

Patients receiving concomitant Enalapril Co 20/12,5 Biotech and neprilysin inhibitor therapy (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.5). The combination of enalapril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of enalapril therapy. If treatment with sacubitril/valsartan is stopped, enalapril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy and bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Anaphylactoid Reactions during Hymenoptera Desensitisation

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

Anaphylactoid Reactions during LDL-Apheresis

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.

Cough

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

Surgery/Anaesthesia

Enalapril blocks angiotensin II formation and therefore impairs the ability of patients undergoing major surgery or anaesthesia with medicines that produce hypotension to compensate via the renin-angiotensin system. Hypotension which occurs due to this mechanism can be corrected by volume expansion (see section 4.5).

Ethnic Differences

Enalapril is apparently less effective in lowering blood pressure in black patients than in non-black patients, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Metabolic and Endocrine Effects

Thiazide therapy, including treatment with hydrochlorothiazide, may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required (see section 4.4). Diabetic patients treated with oral antidiabetic medicines or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see section 4.5).

Thiazides may decrease serum sodium, magnesium and potassium levels.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy; however, at the 12,5 mg dose of hydrochlorothiazide contained in Enalapril Co 20/12,5 Biotech, minimal or no effect was reported.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of latent hyperparathyroidism. Thiazides should be discontinued before testing parathyroid function.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. This effect on hyperuricemia appears to be dose related. In addition, enalapril may increase urinary uric acid and thus may attenuate the hyperuricaemic effect of hydrochlorothiazide.

Anti-doping test

Hydrochlorothiazide contained in this product can produce a positive analytic result in an anti-doping test.

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 exposure has been observed in two epidemiological studies. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide 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 minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. Enalapril Co 20/12,5 Biotech 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).

Fluoroquinolones

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

Eye

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

Sulphonamide derivative medicines 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 medicine 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 sulphonamide or penicillin allergy.

Acute Respiratory Toxicity

Cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Enalapril Co 20/12,5 Biotech should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Lactose

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

Paediatric population

Safety and efficacy in children have not been established.

4.5 Interaction with other medicines and other forms of interaction

Enalapril Maleate-Hydrochlorothiazide

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

Data have 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, 4.4 and 5.1).

Other Antihypertensive medicines

Concomitant use of these medicines may increase the hypotensive effects of enalapril and hydrochlorothiazide. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury. 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).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels due to reduced renal clearance and enhance the risk of lithium toxicity with ACE inhibitors.

Use of Enalapril Co 20/12,5 Biotech with lithium is contraindicated with Enalapril Co 20/12,5 Biotech (see section

4.3).

Allopurinol

The concurrent use of ACE inhibitors, such as enalapril, as in Enalapril Co 20/12,5 Biotech, and allopurinol might increase the risk of neutropenia/agranulocytosis and serious infection especially in renal impairment (section 4.3 and 4.4).

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 medicine. Therefore, the antihypertensive effect of angiotensin II receptor antagonists, ACE inhibitors or diuretics may be attenuated by NSAIDs including selective COX-2 inhibitors.

The coadministration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE inhibitors as in Enalapril Co 20/12,5 Biotech 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.

Enalapril Maleate

Potassium-sparing Diuretics, Potassium Supplements, or other medicine that may increase serum potassium

ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g., spironolactone, eplerenone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes, or other medicine that may increase serum potassium (e.g., heparin, trimethoprim-containing products such as cotrimoxazole) may lead to significant increases in serum potassium. If concomitant use of enalapril and any of the above-mentioned

medicines is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 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 (see sections 4.2 and 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic or by increasing volume or salt intake.

Tricyclic Antidepressants/Antipsychotics/Anaesthetics

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with Enalapril Co 20/12,5 Biotech may result in further reduction of blood pressure (see section 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.

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 4.4).

Neprilysin Inhibitors

Patients receiving concomitant Enalapril Co 20/12,5 Biotech 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).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of Enalapril Co 20/12,5 Biotech (see section 4.5).

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

Antidiabetics (insulin and oral medicines)

Concomitant administration of Enalapril Co 20/12,5 Biotech 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 sections 4.4 and 4.8).

Acetyl Salicylic Acid, Thrombolytics and β-blockers

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

Hydrochlorothiazide

Non-depolarising Muscle Relaxants

Thiazides may increase the responsiveness to tubocurarine.

Alcohol, Barbiturates, or Opioid Analgesics

Potentiation of orthostatic hypotension may occur.

Antidiabetic Medicines (Oral medicines and Insulin)

Dosage adjustment of the antidiabetic medicine may be required (see sections 4.4 and 4.8).

Cholestyramine and Colestipol Resins

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

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

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).

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalaemia.

Kaliuretic Diuretics (e.g., Furosemide), Carbenoxolone, or Laxative Abuse

Hydrochlorothiazide may increase the loss of potassium and/or magnesium.

Pressor Amines (e.g., Noradrenaline)

The effect of pressor amines may be decreased (see section 4.5).

Cytostatics (e.g., Cyclophosphamide, Methotrexate)

Thiazides may reduce the renal excretion of cytotoxic medicine and potentiate their myelosuppressive effects.

When administered concurrently, the following medicines may interact with thiazide diuretics (as in Enalapril Co 20/12,5 Biotech):

Metformin: there is a risk of lactic acidosis when co-administered with hydrochlorothiazide (as in Enalapril Co 20/12,5 Biotech)

Calcium salts: thiazide diuretics, as in Enalapril Co 20/12,5 Biotech, may increase serum calcium levels due to the decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly

Other interactions

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides, as in Enalapril Co 20/12,5 Biotech.

Anticholinergic medicines (e.g., atropine, biperiden) may increase the bioavailability of thiazide-type diuretics, as in Enalapril Co 20/12,5 Biotech, by decreasing gastrointestinal motility and stomach emptying rate.

Thiazides, as in Enalapril Co 20/12,5 Biotech, may increase the risk of adverse effects caused by amantadine.

Administration of thiazide diuretics, as in Enalapril Co 20/12,5 Biotech, with vitamin D may potentiate a rise in serum calcium.

There have been reports in the literature of haemolytic anaemia occurring with concomitant use with hydrochlorothiazide, as in Enalapril Co 20/12,5 Biotech, and methyldopa.

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Patients planning pregnancy should be changed to alternative antihypertensive treatments. When pregnancy is diagnosed, treatment with Enalapril Co 20/12,5 Biotech should be stopped immediately, and, if appropriate, alternative therapy should be started.

Pregnancy

Enalapril Co 20/12,5 Biotech is contraindicated during pregnancy.

Pregnant women should be informed of the potential hazards to the foetus and must not take Enalapril Co 20/12,5 Biotech during pregnancy (see section 4.3). Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spins bifida) and of kidney malformations.

Enalapril Co 20/12,5 Biotech 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 ACE inhibitors [as contained in Enalapril Co 20/12,5 Biotech] during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.

Breastfeeding

Enalapril Co 20/12,5 Biotech is contraindicated during breastfeeding. Both enalapril and thiazides, including hydrochlorothiazide, as in Enalapril Co 20/12,5 Biotech, appear in human milk. If use of Enalapril Co 20/12,5 Biotech is deemed essential, the patient should stop breastfeeding. Hydrochlorothiazide in high doses causing intense diuresis can inhibit the milk production.

Fertility

There are no data on fertility.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that dizziness or weariness may occur (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most common side effects reported were headache and cough.

b. Tabulated list of adverse reactions

The following undesirable side effects have been reported for enalapril maleate:

System organ class	Frequent	Less frequent	Frequency unknown
Blood and lymphatic system disorders		Anaemia (including aplastic and haemolytic), neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy,	
Immune system disorders	Hypersensitivity/ angio-oedema of the face, extremities, lips, tongue, glottis and/or larynx	Autoimmune diseases	
Endocrine disorders			Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders		Hypoglycaemia (see section 4.4), anorexia	Gout
Psychiatric disorder	Depression	Confusion	
Nervous system	Dizziness, headache,	Somnolence, paraesthesia,	

disorders	syncope, taste alterations	vertigo, nervousness, insomnia, dream abnormality, sleep disorders	
Eye disorders	Blurred vision		
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders	Chest pain, rhythm disturbances, angina pectoris, tachycardia	Palpitations, myocardial infarction or cerebrovascular accident*, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	
Vascular disorders	Hypotension (including orthostatic hypotension)	Flushing, orthostatic hypotension, Raynaud's phenomenon	
Respiratory, thoracic, and mediastinal disorders	Cough, dyspnoea	Rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma, pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilia, pneumonia	
Gastrointestinal disorders	Nausea, diarrhoea, abdominal pain	Ileus, pancreatitis, vomiting, dyspepsia, constipation, gastric irritations, dry mouth, peptic ulcer, stomatitis/aphthous ulcerations, glossitis, intestinal angioedema, flatulence	
Hepatobiliary 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, exfoliative dermatitis, toxic epidermal necrolysis, erythroderma, pemphigus	A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.
Musculoskeletal, connective tissue, and bone disorder		Muscle cramps	Arthralgia
Renal and urinary disorder		Renal dysfunction, renal failure, proteinuria	Oliguria
Reproductive system and breast disorders		Impotence, gynecomastia	
General disorder and administration site conditions	Asthenia, fatigue	Malaise, fever	
Investigations	Hyperkalaemia, increases in serum creatinine	Increases in blood urea, hyponatraemia, elevations of liver enzymes, elevations of serum bilirubin	

The following undesirable side effects have been reported for hydrochlorothiazide:

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations			Sialoadenitis
Neoplasm benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancer (Basal cell carcinoma and squamous cell carcinoma
Blood and lymphatic system disorders		Aplastic anaemia, haemolytic anaemia, bone marrow depression, leukopenia, neutropenia, agranulocytosis, thrombocytopenia	
Immune system disorders		Hypersensitivity, allergy, anaphylactic reactions	
Endocrine disorders			Loss of diabetic control
Metabolism and nutrition disorders	Electrolyte imbalance (including hyponatraemia), volume depletion		Anorexia, loss of appetite, hypercholesterolaemia, hyperglycaemia
Psychiatric disorders			Restlessness
Nervous system disorders			Light-headedness
Eye disorders			Xanthopsia, acute myopia, acute angle-closure glaucoma, transient blurred vision
Vascular disorders			Necrotizing angiitis (vasculitis)

Respiratory, thoracic, and mediastinal disorders			Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders		Pancreatitis, stomach upset	Anorexia, gastric irritation
Hepatobiliary disorders		Hepatocellular jaundice, cholestatic jaundice	
Skin and subcutaneous tissue disorders		Cutaneous lupus erythematosus like reactions (or reactivation of lupus erythematosus), photosensitivity reactions, cutaneous vasculitis, toxic epidermal necrolysis	Urticaria, purpura
Musculoskeletal, connective tissue, and bone disorder			Weakness, muscle spasm
Renal and urinary disorder			Interstitial nephritis, renal dysfunction, glycosuria
General disorders			Fever
Investigations			Increase in triglycerides

The following undesirable side effects have been reported for Enalapril Co 20/12,5 Biotech:

System organ class	Frequent	Less frequent	Frequency unknow
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)

Blood and lymphatic system disorders		Decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, decrease in platelets, decrease in white cell count, anaemia (including aplastic and haemolytic), neutropenia, bone marrow depression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases	
Immune system disorders		Hypersensitivity/ angioedema of the face, extremities, lips, tongue, glottis and/or larynx	
Endocrine disorders			Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Hyperglycaemia, hypokalaemia, increase in cholesterol, increase in triglycerides	Hyperuricaemia, gout, hyponatraemia, hypoglycaemia, anorexia	
Psychiatric disorder	Insomnia		
Nervous system disorders	Dizziness, headache, paraesthesia, depression, taste alteration	Nervousness, somnolence, vertigo, paresis (due to hypokalaemia), confusion, 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 (including orthostatic hypotension), syncope	Non-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, vomiting	Dyspepsia, abdominal pain, constipation, flatulence, dry mouth, pancreatitis, ileus, gastric irritations, 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, 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 ANA, elevated ESR, eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.
Musculoskeletal, connective tissue, and bone disorder	Muscle cramps	Arthralgia	
Renal and urinary disorder		Renal dysfunction, renal failure, proteinuria, oliguria, intestinal nephritis	
Reproductive system and breast disorders	Decreased libido, impotence	Gynaecomastia	
General disorder and administration site conditions	Asthenia, fatigue	Fever, malaise	

Investigations		Increases in blood urea, increase in serum creatinine, elevations of liver enzymes, elevations of serum bilirubin, hyperkalaemia.	

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. Health care 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.

4.9 Overdose

No specific information is available on the treatment of overdosage with Enalapril Co 20/12,5 Biotech. Treatment is symptomatic and supportive. Therapy with Enalapril Co 20/12,5 Biotech should be discontinued and the patient observed closely. Suggested measures include induction of emesis, administration of activated charcoal, and administration of a laxative if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures, introduced within 2 hours of ingestion.

Enalapril maleate

The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdosage of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

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 ingestion is recent, take measures aimed at eliminating enalapril

maleate (e.g., emesis, administration of absorbents, and sodium sulfate). If available, angiotensin II infusion and/or intravenous catecholamines may be beneficial. Enalaprilat may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia.

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

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac dysrhythmias.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: 7.1.3 Other hypotensives

Pharmacotherapeutic group: Vascular medicines , ATC code: C09BA02.

Enalapril maleate

Angiotensin-converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE, which leads to increased plasma renin activity (due to removal of negative feedback on renin release), and decreased aldosterone secretion.

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

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure, enalapril is

antihypertensive even in patients with low-renin hypertension.

Enalapril maleate - hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive medicine which increases plasma renin activity. Although enalapril alone is antihypertensive even in patients with low-renin hypertension, concomitant administration of hydrochlorothiazide in these patients leads to greater reduction of blood pressure.

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.

Biotransformation

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

Absorption

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.

Biotransformation

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

Pregelatinised starch

Maleic acid

Iron oxide yellow

Dried maize starch

Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blister packs: 3 years

HDPE container: 2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original container until required for use.

6.5 Nature and contents of container

Enalapril Co 20/12,5 Biotech are packed into either

- Aluminium / Aluminium Blisters of 10 tablets; the blisters are then packed in an outer carton containing 30 tablets.
- HDPE container as 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark

Midrand

1685

8. REGISTRATION NUMBER(S)

56/7.1.3/0184

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2023

10. DATE OF REVISION OF THE TEXT

10 October 2023