Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ENALAPRIL 5 BIOTECH tablets

ENALAPRIL 10 BIOTECH tablets

ENALAPRIL 20 BIOTECH tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ENALAPRIL 5 BIOTECH: Each tablet contains enalapril maleate 5,0 mg.

ENALAPRIL 10 BIOTECH: Each tablet contains enalapril maleate 10,0 mg.

ENALAPRIL 20 BIOTECH: Each tablet contains enalapril maleate 20,0 mg.

Contains sugar (lactose monohydrate: 232,00 mg per 5 mg tablet, 142,00 mg per 10 mg tablet and 284,00 mg per 20 mg tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

ENALAPRIL 5 BIOTECH: Pink, mottled, round, flat tablets with bevelled edges, debossed with “ELP 5” on one side and scored on the other side.

ENALAPRIL 10 BIOTECH: Brownish-pink, mottled, round, flat tablets with bevelled edges, debossed with “ELP 10”.

ENALAPRIL 20 BIOTECH: Greyish-violet, mottled, round, flat tablets with bevelled edges, debossed with “ELP 20”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENALAPRIL BIOTECH is indicated in:

Hypertension: Essential hypertension.

Heart Failure: The treatment of symptomatic congestive heart failure, usually in combination with diuretics and digoxin. In these patients ENALAPRIL BIOTECH improves symptoms, increases survival, and decreases the frequency of hospitalisation.

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

4.2 Posology and method of administration

Posology

Treatment for hypertension

The initial dose is 10 mg to 20 mg depending on the degree of hypertension and is given once daily. In mild hypertension the recommended initial dose is 10 mg daily. For other degrees of hypertension, the initial dose is 20 mg daily. The usual maintenance dose is one 20 mg tablet taken once daily. The dosage should be adjusted according to the needs of the patient.

Concomitant diuretic therapy in hypertension

Symptomatic hypotension may occur following the initial dose of ENALAPRIL BIOTECH; this is more likely in patients who are being treated currently with diuretics.

Caution is therefore recommended since these patients may be volume or salt depleted. The diuretic therapy should be discontinued for 2 – 3 days prior to the initiation of therapy with ENALAPRIL BIOTECH. If this is not possible, the initial dose of ENALAPRIL BIOTECH should be low (5 mg or less) to determine the initial effect on the blood pressure. Dosage should then be

adjusted according to the needs of the patient.

Dosage in renal insufficiency

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

Renal status	**Creatine clearance mL/min**	**Initial dose mg/kg**
Mild impairment	50 – 80	5
Moderate impairment	< 50 – 30	2,5

Heart failure/asymptomatic left ventricular dysfunction

The initial dose of ENALAPRIL BIOTECH in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2,5 mg daily and it should be administered under close medical supervision to determine the initial effect on blood pressure.

In the absence of, or after effective management of symptomatic hypotension following initiation of therapy with ENALAPRIL BIOTECH in congestive heart failure, the dose should be gradually increased, depending on the patient's response to the usual maintenance dose (10 to 20 mg) in a single or divided dose.

This dose titration may be performed over a 2 to 4 week period, or more rapidly if indicated by the presence of residual signs and symptoms of heart failure.

Blood pressure and renal function should be monitored closely before and after starting treatment with ENALAPRIL BIOTECH (see section 4.4), because hypotension and consequent renal failure have been reported.

In patients treated with diuretics, the dosage should be reduced if possible before beginning treatment with ENALAPRIL BIOTECH.

The appearance of hypotension after the initial dose of ENALAPRIL BIOTECH does not imply that

hypotension will occur during chronic therapy with ENALAPRIL BIOTECH and does not preclude continued use of ENALAPRIL BIOTECH.

Serum potassium should also be monitored (see section 4.5).

Method of administration

Oral use.

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

4.3 Contraindications

- Hypersensitivity to enalapril maleate or to any of the excipients listed in section 6.1.
- Patients with a history of angioedema relating to previous ACE-inhibitor therapy or angiotensin receptor blocker: These 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).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with ENALAPRIL BIOTECH may lead to toxic blood concentrations of lithium (see section 4.5).
- Concomitant use of fluoroquinolones with ENALAPRIL BIOTECH is contraindicated in patients with moderate to severe renal impairment.
- Pregnancy and lactation (see section 4.6).

- The concomitant use of ENALAPRIL BIOTECH with aliskiren-containing products is contraindicated (see sections 4.4 and 4.5).
- Concomitant use with sacubitril/valsartan therapy. ENALAPRIL BIOTECH must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving ENALAPRIL BIOTECH, the treatment must be stopped promptly and changed to a different class of antihypertensive medicine (see section 4.6). If a woman is contemplating pregnancy, a different class of medicine should be used (see section 4.6).

ENALAPRIL BIOTECH should be used with caution in the following conditions:

Cerebrovascular disease or ischaemic heart disease

Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular accidents. Therapy should be monitored patients with ischaemic heart disease or cerebrovascular disease especially when the dose of ENALAPRIL BIOTECH or diuretic is adjusted.

Symptomatic hypotension

Symptomatic hypotension may occur in patients with uncomplicated hypertension. Hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see sections 4.5 and 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia 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 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 myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of 0,9 % sodium chloride. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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

Surgery/anaesthesia

Hypotension may occur in patients undergoing major surgery or during anaesthesia, since enalapril, as contained in ENALAPRIL BIOTECH, blocks angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Aortic stenosis/hypertrophic cardiomyopathy

ENALAPRIL BIOTECH should not be given to patients with obstruction in the outflow tract of the left ventricle because cardiac output cannot increase to compensate for systemic vasodilatation and there is a severe risk of hypotension (see section 4.3).

Renal function impairment

Older patients with congestive heart failure are particularly susceptible to ACE inhibitor-induced acute renal failure.

Renal artery stenosis, bilateral or in one kidney or renal transplant: There is an increased risk of renal function impairment, increased blood urea and serum creatinine concentrations (see section 4.3).

Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when ENALAPRIL BIOTECH has been given concomitantly with a diuretic. Dosage reduction or discontinuation of ENALAPRIL BIOTECH or the diuretic may be required.

Renovascular disease – ENALAPRIL BIOTECH should not be used in patients with renovascular disease or suspected renovascular disease but it may be used cautiously in severe resistant hypertension in such patients. In this instance ENALAPRIL BIOTECH should only be used under specialist supervision. The elderly, patients with peripheral vascular diseases or generalised atherosclerosis may have asymptomatic renovascular disease (see section 4.2).

Concomitant use of fluoroquinolones and ACE inhibitors/renin-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/renin-angiotensin receptor blockers.

Hepatic failure

ACE inhibitors, such as ENALAPRIL BIOTECH, 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 BIOTECH who develop jaundice or marked elevations of hepatic enzymes should discontinue the ENALAPRIL BIOTECH and receive appropriate medical follow-up.

Agranulocytosis/Neutropenia

Patients with bone marrow depression have an increased risk for developing agranulocytosis and

neutropenia.

Severe autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma increase the risk for development of neutropenia or agranulocytosis.

There is also an increased risk of agranulocytosis and neutropenia when immunosuppressants are concurrently administered.

Regular white blood cell counts may be necessary in patients with collagen vascular disorders or patients receiving immunosuppressive therapy, especially if these patients also have impaired renal function.

Cough

Cough has been reported with the use of ACE-inhibitors, including ENALAPRIL BIOTECH. 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.

Myocardial infarction

In acute myocardial infarction, treatment with ENALAPRIL BIOTECH should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 µmol/L or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 µmol/L or doubling of the pre-treatment value) then ENALAPRIL BIOTECH may need to be withdrawn (see also section 4.3).

In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.

Hypotension in acute myocardial infarction - Treatment with ENALAPRIL BIOTECH must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 98 mmHg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose

should be reduced if the systolic blood pressure is 120 mmHg or lower.

Maintenance doses should be reduced if systolic blood pressure is 98 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg) for more than 1 hour then ENALAPRIL BIOTECH should be withdrawn.

Diabetic patients

Diabetic patients receiving oral hypoglycaemics or insulin are at an increased risk of developing severe hypoglycaemia.

Hyperkalaemia

Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride may lead to hyperkalaemia and is therefore contraindicated (see section 4.3).
Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus and concomitant use of potassium supplements or potassium-containing salt substitutes.
The use of potassium supplements or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause cardiac conduction abnormalities, dysrhythmias and cardiac arrest (see section 4.5).

Hypersensitivity/angioedema

If angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients treated with ENALAPRIL BIOTECH, ENALAPRIL BIOTECH should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms and should never again receive this class of medicine.
Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered. This may include the administration of epinephrine (adrenaline) and/or the maintenance of a patent airway. The patient should be under close medical supervision until

complete and sustained resolution of symptoms has occurred. These patients should never receive any ENALAPRIL BIOTECH or any medicine of this class again.

ENALAPRIL BIOTECH causes a higher rate of angioedema in black patients than in non-black patients.

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

Concomitant use of ENALAPRIL BIOTECH with sacubitril/valsartan is contraindicated due to the increased risk of angioedema.

Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of ENALAPRIL BIOTECH. Treatment with ENALAPRIL BIOTECH must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ENALAPRIL BIOTECH with racecadotril, mTOR inhibitors (e.g., sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor such as ENALAPRIL BIOTECH.

Anaphylactoid reactions during hymenoptera desensitisation

Anaphylactoid reactions have occurred in patients using ACE inhibitors such as ENALAPRIL BIOTECH during desensitising protocols involving for example, hymenoptera venom. These reactions can be avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitisation.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulfate absorption and treated

concomitantly with an ACE-inhibitor, including ENALAPRIL BIOTECH. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive medicine.

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 ENALAPRIL BIOTECH and aliskiren is therefore contraindicated (see section 4.3).
ENALAPRIL BIOTECH should not be used concomitantly with aliskiren (see section 4.3).

Paediatric population

Safety and efficacy in children have not been established.

Excipients

ENALAPRIL BIOTECH contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ENALAPRIL BIOTECH.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3). The interaction may lead to renal impairment due to altered renal haemodynamics. Increased serum creatinine and blood urea nitrogen have been observed.

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

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

Anti-hypertensive therapy

The combination of ENALAPRIL BIOTECH with other antihypertensive medicines, diuretics or alcohol may increase the antihypertensive effect. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.

“First dose hypotension” may occur with concurrent use of ENALAPRIL BIOTECH and loop, thiazide or related diuretics (see sections 4.2 and 4.3).

The hypotensive effects of ENALAPRIL BIOTECH may be potentiated by the combination of ENALAPRIL BIOTECH with beta-adrenergic blocking medicines and methyldopa or calcium channel blockers.

Ganglion blocking medicines or adrenergic blocking medicines, combined with ENALAPRIL BIOTECH, should only be given with careful observation of the patient.

Non-steroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors (COX-2)

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective COX-2 inhibitors may reduce the antihypertensive effects of ENALAPRIL BIOTECH. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with ENALAPRIL BIOTECH.

In patients with compromised renal function who are being treated with NSAIDs, the concurrent use of ENALAPRIL BIOTECH may result in a further deterioration of renal function. These effects are usually reversible.

Serum potassium

Risk factors for the development of hyperkalaemia during concurrent treatment with ENALAPRIL BIOTECH include renal insufficiency, diabetes mellitus and concurrent use of potassium supplements, or potassium-containing salt substitutes.

Frequent monitoring of serum potassium should be done in these patients (see section 4.4).

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors 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. In diabetic patients treated with oral antidiabetic medicines or insulin, glycaemic control should be closely monitored for hypoglycaemia.

Serum lithium

Because of the reduction in lithium elimination, increases in lithium concentrations to toxic levels have been reported (see see section 4.3).

Tricyclic antidepressants/antipsychotics/anaesthetics/narcotics

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ENALAPRIL BIOTECH may result in further reduction of blood pressure.

Antacids

Concurrent use of antacids may reduce bioavailability of ENALAPRIL BIOTECH.

Ciclosporin

An additive hyperkalaemic effect with concurrent use of ENALAPRIL BIOTECH and ciclosporin is possible.

Gold salts

Concurrent treatment with gold salts such as sodium aurothiomalate and ENALAPRIL BIOTECH may lead to patients experiencing nitritoid reactions (facial flushing, nausea, vomiting and hypotension).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ENALAPRIL BIOTECH.

Epoetins

Concurrent use of epoetins and ENALAPRIL BIOTECH may lead to an additive hyperkalaemic effect. ENALAPRIL BIOTECH also antagonises the haematopoietic effects of epoetin.

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ENALAPRIL BIOTECH is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take ENALAPRIL BIOTECH 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 ENALAPRIL BIOTECH 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 spins bifida) and of kidney malformations.

ENALAPRIL 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 ENALAPRIL BIOTECH during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3)

Breastfeeding

The use of ENALAPRIL BIOTECH is contraindicated during breastfeeding (see section 4.3).

Enalapril and enalaprilat are secreted in human milk.

4.7 Effects on ability to drive and use machines

Caution when driving or performing tasks requiring alertness because of possible dizziness, somnolence and fatigue.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: Decreases in white blood cell count, haemoglobin and haematocrit, bone marrow depression, anaemia (including aplastic and haemolytic), thrombocytopenia, neutropenia, pancytopenia, agranulocytosis, elevated erythrocyte sedimentation rate, eosinophilia, lymphadenopathy, leucocytosis and autoimmune diseases.

Immune system disorders

Less frequent: Hypersensitivity/angioedema reactions: angioedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx and intestinal angioedema.

Metabolism and nutrition disorders

Less frequent: Cases of hypoglycaemia in diabetic patients on oral antidiabetic medicines or insulin have been reported (see section 4.5), anorexia.

Psychiatric disorders

Frequent: Depression.

Less frequent: Mood alterations, mental confusion, nervousness, insomnia, dream abnormality, sleep disorders.

Nervous system disorders

Frequent: Dizziness, headache, taste disturbances.

Less frequent: Paraesthesia, vertigo, somnolence, syncope.

Eye disorders

Frequent: Blurred vision.

Ear and labyrinth disorders

Less frequent: Tinnitus.

Cardiac disorders

Frequent: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see section 4.4), chest pain rhythm disturbances, angina

pectoris, tachycardia.

Less frequent: Palpitations.

Vascular disorders

Frequent: Hypotension (including orthostatic hypotension).

Less frequent: Orthostatic hypotension, flushing, Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders

Frequent: Cough, dyspnoea.

Less frequent: Bronchospasm/asthma, rhinitis, sinusitis, rhinorrhoea, sore throat, hoarseness, pulmonary infiltrates, allergic alveolitis, pneumonia.

Gastrointestinal disorders

Frequent: Diarrhoea, nausea, abdominal pain.

Less frequent: Dyspepsia, dry mouth, pancreatitis, vomiting, ileus, constipation, stomatitis/aphthous ulcerations, glossitis, intestinal angioedema, constipation, gastric irritations, peptic ulcer, anorexia.

Frequency unknown: Tongue ulcers.

Hepato-biliary disorders

Less frequent: Hepatitis (hepatocellular or cholestatic) including necrosis, cholestasis (including jaundice), hepatic failure.

Skin and subcutaneous tissue disorder

Frequent: Rash, angioedema of the face, extremities, lips, tongue, glottis and/or larynx (see section 4.4).

Less frequent: Urticaria, diaphoresis, alopecia, pruritus, psoriasis, severe skin disorders including

pemphigus, erythroderma, toxic epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson syndrome and erythema multiforme.

Musculoskeletal and connective tissue disorders

Less frequent: Muscle cramps.

Frequency unknown: Severe muscle pain (and weakness), accompanied by morning stiffness (symptoms resolve within few days of stopping ENALAPRIL BIOTECH treatment).

Renal and urinary disorders

Less frequent: Uraemia, oliguria, anuria, renal dysfunction, renal failure, proteinuria.

Reproductive system and breast disorders

Less frequent: Impotence, gynecomastia.

General disorders and administration site conditions

Frequent: Fatigue, asthenia.

Less frequent: Malaise, fever.

Investigations

Frequent: Hyperkalaemia, increases in serum creatinine

Less frequent: Hyponatraemia, increases in blood urea, increases in liver enzymes, increases in serum bilirubin.

Post-marketing experience

Endocrine disorders: Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Skin and subcutaneous tissue disorders: A symptom complex has been reported which may include: fever, serositis, vasculitis, myalgia/myositis, arthritis/arthralgia, a positive antinuclear

antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ENALAPRIL BIOTECH is important. It allows continued monitoring of the benefit/risk balance of ENALAPRIL BIOTECH. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Adverse Drug Reactions Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

(See section 4.8)

Limited data are available for overdosage in humans.

The most prominent feature of overdosage is marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor.

The main adverse effect is hypotension therefore the recommended treatment of overdosage is intravenous infusion of normal saline solution and supportive treatment.

Enalaprilat may be removed from the general circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A.7.1.3 Other hypotensives.

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A02.

5.1 Pharmacodynamic properties

Enalapril maleate inhibits angiotensin I-converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels result in

a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium.

It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

5.2 Pharmacokinetic properties

Absorption

The extent of absorption after oral administration is 60 % (not reduced by food) with wide variability between patients.

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor.

The time to achieve peak serum concentration is within an hour for enalapril maleate and 3 – 4 hours for enalaprilat.

The plasma half-life is 1,3 hours for enalapril maleate and 11 hours for the active metabolite, enalaprilat, which is increased in renal impairment.

Distribution

Over the range of concentrations which are therapeutically relevant, enalaprilat binding to human plasma proteins does not exceed 60 %.

Biotransformation

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

Elimination

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40 % of the dose, and intact enalapril (about 20 %).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ENALAPRIL 5 BIOTECH:

Croscarmellose sodium

Ferric oxide (red)

Lactose monohydrate

Magnesium stearate

Maize starch

Pregelatinised starch

Sodium hydrogen carbonate.

ENALAPRIL 10 BIOTECH and ENALAPRIL 20 BIOTECH:

Croscarmellose sodium

Ferric oxide (black)

Ferric oxide (red)

Lactose monohydrate

Magnesium stearate

Maize starch

Pregelatinised starch

Sodium hydrogen carbonate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a dry place, at or below 25 °C. Protect from moisture.

6.5 Nature and contents of container

Aluminium foil blister packs containing 20, 30 and 90 tablets.

6.6 Special precautions for disposal and other handling

No additional information.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor Block K West Central Park

400 16th Road, Randjespark

Halfway House

Midrand 1685

8. REGISTRATION NUMBERS:

ENALAPRIL 5 BIOTECH: 37/7.1.3/0330

ENALAPRIL 10 BIOTECH: 37/7.1.3/0331

ENALAPRIL 20 BIOTECH: 37/7.1.3/0332

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 February 2016

10. DATE OF REVISION OF THE TEXT

2 December 2022