PROFESSIONAL INFORMATION

ENAP RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ENAP 5 mg tablets

ENAP 10 mg tablets

ENAP 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ENAP 5 mg: Each tablet contains 5 mg enalapril maleate.

ENAP 10 mg: Each tablet contains 10 mg enalapril maleate.

ENAP 20 mg: Each tablet contains 20 mg enalapril maleate.

ENAP contains sugar (lactose monohydrate 129,80 mg, 124,60 mg and 117,80 mg in ENAP 5 mg, 10 mg and 20 mg respectively).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

ENAP 5 mg: Round, flat, white tablets, bevel-edged scored on one side.

ENAP 10 mg: Round, flat, red-brown tablets, bevel-edged, scored on one side, with individual white spots.

ENAP 20 mg: Round, flat, light orange tablets, bevel-edged, scored on one side, with individual white spots.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENAP is indicated for:

Hypertension

Essential hypertension - all grades.

Renovascular hypertension.

Heart failure

Treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients, symptom improvement, survival increase, and decrease frequency of hospitalization were observed (see section 5).

Asymptomatic Left Ventricular Dysfunction

In asymptomatic patients, with left ventricular dysfunction (ejection fraction < 35 %), who are clinically stable, the rate of development of overt heart failure and incidence of hospitalization for heart failure are decreased (see section 5).

4.2 Posology and method of administration

ENAP may be administered before, during or after meals as its absorption is not affected by food intake.

Essential Hypertension:

Depending on the degree of hypertension, an initial dose of 10 to 20 mg is given once daily. The recommended initial dose in mild hypertension is 10 mg daily. An initial dose of 20 mg daily should be used for other degrees of hypertension. The usual maintenance dose is one 20 mg tablet taken once daily. Dosage should be adjusted to the patient's needs.

Renovascular Hypertension:

Blood pressure and renal function in patients with renovascular hypertension may be particularly sensitive to ACE-inhibition, therefore, a lower starting dose (e.g. 5 mg or less) should be used to initiate therapy. Dosage adjustment should be made according to the needs of the patient. The majority of patients may be expected to respond to one 20 mg tablet, taken once daily. Caution is

recommended in patients with hypertension who have been treated recently with diuretics. (See paragraph below).

Concomitant Diuretic Therapy in Hypertension:

Following the initial dose of ENAP, symptomatic hypotension may occur; such reactions are more likely to occur in patients receiving concomitant diuretic treatment.

As these patients may be volume or salt depleted, caution is recommended during administration of ENAP. Diuretic therapy should be discontinued for 2 - 3 days prior to initiation of therapy with ENAP. If this is not possible, a low initial dose (5 mg or less) should be used to assess the initial effect on the patient's blood pressure. Dosage should then be adjusted according to the patient's needs.

Heart Failure/Asymptomatic Left Ventricular Dysfunction:

In patients with symptomatic heart failure or asymptomatic left ventricular dysfunction, an initial dose of 2,5 mg should be used. Close medical supervision is necessary to determine the initial effect on blood pressure. After initiation of therapy with ENAP in heart failure, provided symptomatic hypotension is absent, or has been effectively managed, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, depending on patient tolerance.

This dose titration should be carried out over a 2 - 4 week period, or more rapidly if residual signs and symptoms of heart failure are present. This dosage regimen is effective in reducing mortality in patients with symptomatic heart failure.

Care must be taken to monitor blood pressure and renal function closely before and after starting treatment with ENAP (see section 4.4), because hypotension followed by renal failure has been reported. In patients receiving treatment with diuretics, the dosage of the diuretic should, if possible, be reduced before treatment with ENAP is initiated. If hypotension should occur after the initial dose of ENAP, it does not imply that hypotension will recur during chronic ENAP therapy, nor preclude continued use of ENAP.

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

Special populations

Dosage in Renal Insufficiency:

In general, the intervals between ENAP administration should be prolonged and/or a reduced dosage should be administered.

Renal status	Creatinine Clearance mL/min	Initial Dose mg/day
Mild impairment	< 80 > 30	5
Moderate impairment	< 30 > 10	2,5
Severe impairment Normally these patients will be on dialysis*	< 10	2,5 mg on dialysis days **

*See section 4.4 – Haemodialysis Patients

** Enalaprilat is dialysable. Dosage on non-dialysis days should be adjusted depending on the blood pressure response.

Paediatric population

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

Method of administration

Oral use.

Missed dose:

Doctors should advise patients who forget to take ENAP 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 or to any of the ingredients of ENAP (see section 6.1).
- Concomitant use of fluoroquinolones with ACE inhibitors, such as ENAP is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance less than or equal
- to 30 mL/min) and in elderly patients.
- 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).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as eplerenone, spironolactone, triamterene, amiloride.
- Porphyria.
- Anuria.
- Severe hepatic impairment.
- Lithium therapy: Concomitant administration with ENAP may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see sections 4.4 and 4.6).
- The concomitant use of ENAP with aliskiren-containing products is contraindicated (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman either become pregnant, or contemplate pregnancy, while receiving ENAP, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Safety in pregnancy and lactation has not been established (see section 4.3).

ENAP can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the 2nd and 3rd trimesters (see sections 4.3 and 4.6).

Concomitant use of fluoroquinolones and ACE inhibitors, such as ENAP, 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 fluroquinolones or ACE inhibitors, such as ENAP, whether used separately and/or concomitantly.

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 decrease renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ENAP and aliskiren is therefore contraindicated (see section 4.3).

ENAP should not be used concomitantly with aliskiren (see section 4.3).

Aortic stenosis/hypertrophic cardiomyopathy:

ENAP should not be given to patients with obstruction in the outflow tract of the left ventricle and avoided in cases of haemodynamically significant obstruction and cardiogenic shock (see section 4.3).

Renal function impairment:

Where appropriate, assessment of renal function prior to initiation of, and during treatment with ENAP should be included in the evaluation of the patient.

Enalapril, as contained in ENAP, has been associated with renal failure mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis (see section 4.3). This renal failure is usually reversible, if recognized promptly and immediately treated.

Reduced and/or less frequent doses of ENAP may be required for patients with renal insufficiency (see section 4.2). Renal function should be monitored before and during therapy in those patients with renal insufficiency.

Increases of blood urea and serum creatinine have been observed in some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney (see section 4.3). Patients with renal insufficiency are more likely to develop these symptoms.

Minor and usually transient increases in blood urea and serum creatinine have been observed in some patients with no apparent pre-existing renal disease when ENAP has been given concomitantly with a diuretic. Dosage reduction of ENAP and/or discontinuation of the diuretic may be required.

Kidney transplantation:

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

Renovascular hypertension:

ENAP is contraindicated in renovascular hypertension (see section 4.3).

Neutropenia, agranulocytosis:

Anaemia, neutropenia/agranulocytosis and thrombocytopenia have been reported in patients receiving ACE inhibitors. Neutropenia occurs rarely in patients with normal renal function and no other complications.

In patients with collagen vascular disease, immunosuppressant treatment, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially pre-existing impaired renal function, ENAP should be used with extreme caution.

Serious infections which, in a few instances, did not respond to intensive antibiotic therapy, have been reported in some of these patients.

If these patients are treated with ENAP, periodic monitoring of white blood cells is recommended, and patients are advised to report any signs of infection.

Hyperkalaemia:

In patients treated with ACE inhibitors, including enalapril as contained in ENAP, increases in serum potassium have been reported. Risk factors which may lead to the development of hyperkalaemia include: age (> 70 years old), worsening of renal function, renal insufficiency, diabetes mellitus, dehydration, acute cardiac decompensation and metabolic acidosis.

Concomitant use of ENAP with the following may also cause an elevation in serum potassium: potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes or other medicines associated with increases in serum potassium (e.g. heparin, co-trimoxazole). Serious arrhythmias, sometimes fatal, can occur as a result of hyperkalaemia.

Concomitant treatment of ENAP and any of the above mentioned medicines should be given with caution, and serum potassium levels frequently monitored (see section 4.5). Patients with impaired renal function are particularly prone to a significant increase in serum potassium.

Diabetics:

When starting with an ACE inhibitor, such as enalapril contained in ENAP, diabetic patients treated with insulin or oral diabetic agents should closely monitor for hypoglycaemia, especially during the first month of combined used.

Hypersensitivity/angioneurotic oedema:

Patients may be at increased risk of angioedema while receiving an ACE inhibitor, such as ENAP, if they have a history of angioedema unrelated to ACE inhibitor therapy (see section 4.3).

In some patients treated with ACE inhibitors, including ENAP, angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported. In such cases, ENAP should be

discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms before patients are discharged. In cases where swelling has been confined to the face and lips the condition generally resolves without treatment, although antihistamines have been useful in relieving symptoms.

Angioneurotic oedema associated with laryngeal oedema may be fatal. Where airway obstruction could occur due to involvement of the tongue, glottis or larynx, prompt administration of appropriate therapy such as subcutaneous adrenaline solution 1:1 000 (0,3 mL - 0,5 mL) is indicated.

A higher incidence of angioedema has been reported in black patients receiving ENAP compared to non-black patients.

Anaphylactoid reactions:

Less frequently, patients receiving ACE inhibitors during desensitisation with Hymenoptera venom (e.g. bee or wasp venom) or during low density lipoprotein (LDL)-apheresis with dextran sulphate, have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitization.

Haemodialysis patients: Anaphylactoid reactions have been observed in patients dialysed with high-flux membranes (e.g. AN 69®) concomitantly receiving an ACE inhibitor. Consideration

should be given to using a different type of dialysis membrane or a different class of antihypertensive medicine in these patients.

Cough:

Cough has been reported with the use of ACE inhibitors, such as enalapril contained in ENAP. 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.

Hepatic failure:

ACE inhibitors, such as enalapril contained in ENAP, have been linked to a syndrome which starts with hepatitis or cholestatic jaundice and progresses to fulminant hepatic necrosis and sometimes death. Patients should discontinue treatment with ENAP and receive medical follow-up if they develop jaundice or marked elevations of hepatic enzymes.

Serum potassium:

See section 4.5.

Surgery/anaesthesia:

Enalapril, as contained in ENAP, is known to block angiotensin II formation secondary to compensatory renin release in patients undergoing major surgery or during anaesthesia with agents 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.

Symptomatic hypotension:

Symptomatic hypotension has been observed in uncomplicated hypertensive patients. Hypotension is more likely to occur in hypertensive patients receiving ENAP 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). Symptomatic hypotension has been recorded in patients with heart failure, with or without associated renal insufficiency. It is more likely to develop in patients with more severe degrees of heart failure, reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment. In these patients, therapy should be initiated under medical supervision and whenever the dose of ENAP and/or diuretic is adjusted, these patients should be carefully monitored. In patients with ischaemic heart or cerebrovascular disease in whom an excessive decrease in blood pressure could cause myocardial infarction or cerebrovascular accident, similar precautions should be applied.
If hypotension occurs, the patient should be made to lie down and, if necessary, an intravenous infusion of normal saline should be administered. A transient hypotensive response is not a contraindication to further doses which can be given usually without further problems, once the blood pressure has improved by volume expansion.

In some congestive heart failure patients who have normal or low blood pressure, use of ENAP may result in additional lowering of systemic blood pressure. This effect should be anticipated and is usually not a reason to discontinue treatment. In cases where hypotension becomes symptomatic, it may become necessary to reduce or discontinue treatment with ENAP (see section 4.2).

Ethnic differences:

Possibly due to a higher prevalence of low-renin state in the black hypertensive population, ENAP is less effective in lowering blood pressure in black people than in non-black people.

ENAP 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.

Paediatric population

No studies with ENAP have been carried out with children.

4.5 Interaction with other medicines and other forms of interaction

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).

Fluoroquinolones:

Concomitant use of fluoroquinolones and ACE inhibitors, such as ENAP 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).

Medicines increasing the risk of angioedema:

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema.

Concomitant use of ACE inhibitors with antidiarrheal (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increase risk of angioedema.

Serum Lithium:

Lithium elimination may be reduced (see section 4.3). Therefore if lithium salts are to be administered with ENAP, serum lithium levels should be carefully monitored.

Antihypertensive Therapy:

The combination of ENAP with other antihypertensive medicines, particularly diuretics, may increase the antihypertensive effect.

The hypotensive effects of ENAP are potentiated by combination with beta adrenergic blocking agents and methyldopa or calcium entry blockers.

If ganglionic blocking agents or adrenergic blocking agents are combined with ENAP, the patient should be carefully observed.

No experience of the concomitant use of ENAP with calcium antagonists is currently available; therefore this combination is not recommended.

Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may increase the risk of hypotension.

Serum Potassium:

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.

The administration of ENAP to patients with renal failure, may lead to elevation of serum potassium. A significant increase in serum potassium can occur with the use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes, particularly in patients with impaired renal function (see section 4.3).

Care should also be taken when ENAP is co-administered with other medicines that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/ sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride.

If concomitant use of the medicines mentioned above is deemed necessary, they should be used with caution and serum potassium should be monitored frequently.

Diuretics (hydrochlorothiazide or loop diuretics):

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

Tricyclic antidepressants/antipsychotics/anaesthetics:

Taking certain anaesthetics, antipsychotics and tricyclic antidepressants concurrently with ENAP may further reduce blood pressure (see section 4.4).

Gold:

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

Sympathomimetics:

The antihypertensive effect of ENAP may be reduced by sympathomimetics. Careful monitoring of blood pressure should occur during concomitant use.

Alcohol:

The hypotensive effect of ENAP is enhanced by alcohol.

Antidiabetics:

An increased blood-glucose lowering effect with risk of hypoglycaemia may be caused by concurrent administration of ENAP 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.

Nonsteroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors:

Nonsteroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), may reduce the antihypertensive effect of ENAP.

The co-administration of ENAP with NSAIDs (COX-2 inhibitors) exerts an additive effect on the increase in serum potassium in patients with renal insufficiency and may result in further deterioration of renal function. The effects are normally 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. Patients should be adequately hydrated, and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter.

Other interactions:

Concomitant administration of allopurinol, cytostatic or immuno-suppressive agents, systemic corticosteroids or procainamide with ENAP may increase the risk for leukopenia (see section 4.4. Neutropenia/Agranulocytosis).

Concomitantly administered cyclosporin increases the risk of hyperkalaemia with ENAP.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ENAP is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take ENAP during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative antihypertensive treatment which has been established. ENAP 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 kidney malformations.

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

Oligohydramnios, as well as hypotension, oliguria and anuria in new-borns have been reported after administration of ENAP, 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

Enalapril and enalaprilat are secreted into the breast milk.

The use of ENAP is contraindicated whilst breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Decreases in haemoglobin and haematocrit, anaemia (including aplastic and

		haemolytic), neutropenia, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases
Immune system disorders	Less frequent	Angioneurotic oedema of the face extremities, lips, tongue, glottis and/or larynx, rash
Endocrine disorders	Less frequent	Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Metabolism and nutrition disorders	Less frequent	Hypoglycaemia
Psychiatric disorders	Frequent	Depression
Nervous system disorders	Frequent Less frequent	Headache, taste alteration Confusion, dream abnormality, insomnia, nervousness, paraesthesia, somnolence, vertigo
Eye disorders	Frequent	Blurred vision
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent Less frequent	Chest pain, rhythm disturbance, angina pectoris, tachycardia Myocardial infarction or cerebrovascular accident, these reactions may be secondary to excessive hypotension in high risk patients (see section 4.4)
Vascular disorders	Frequent Less frequent	Dizziness, hypotension (including orthostatic hypotension), syncope Orthostatic hypotension, palpitations, flushing, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Cough, dyspnoea Bronchospasm/asthma, pulmonary infiltrates, rhinorrhoea, sore throat, hoarseness, rhinitis, allergic alveolitis/eosinophilia pneumonia
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain, diarrhoea, nausea, taste disturbances Anorexia, constipation, dyspepsia, glossitis, ileus, intestinal angioedema, pancreatitis, stomatitis/aphthous ulcerations, vomiting, gastric irritations, dry mouth, peptic ulcer
Hepatobiliary disorders	Less frequent	Hepatic failure, hepatitis - either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice)
Skin and subcutaneous tissue disorders	Frequent Less frequent	Rash Alopecia, diaphoresis, erythema multiforme, exfoliative dermatitis, pemphigus, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria A symptom complex, which may include fever, serositis, vasculitis, myalgia, myositis, arthralgia/arthritis, a positive anti-nuclear antibody elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis, has been reported. Dermatologic manifestations, such as rash or photosensitivity may occur.

Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscle cramps
Renal and urinary disorders	Less frequent	Renal dysfunction, renal failure, proteinuria, oliguria
Reproductive system and breast disorders	Less frequent	Impotence, gynecomastia
General disorders and administrative site conditions	Frequent Less frequent	Asthenia, fatigue Malaise, fever
Investigations	Frequent Less frequent	Hyperkalaemia, serum creatinine increases Blood urea increases, hyponatremia, raised liver enzymes and/or serum bilirubin levels, these findings are usually reversible upon discontinuation of ENAP

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 using either of the following links:

https://www.sahpra.org.za/Publications/Index/8 or http://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/

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

4.9 Overdose

Data on overdosage in humans is limited. The major features of overdosage reported to date are marked hypotension, which commences approximately six hours after ingestion of ENAP,

resulting from blockade of the renin-angiotensin system, and stupor.

Signs and symptoms:

Symptoms associated with an overdose of an ACE inhibitors, as contained in ENAP, include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

Management of overdose:

Intravenous infusion of normal saline solution is the treatment of choice for overdosage. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g. emesis, administration of absorbents and sodium sulphate).

Haemodialysis can be used to remove ENAP from the general circulation.

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

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin Converting Enzyme (ACE) inhibitor

ATC code: C09AA02

Pharmacological classification: A 7.1.3 Vascular medicines - other hypotensives.

Mechanism of action

Enalapril maleate is the maleate salt of enalapril, which is a derivative from the amino acids, L-alanine and L-proline. After oral absorption, enalaprilat is formed by hydrolyzation of enalapril maleate. Enalaprilat is a specific, long-acting, non-sulphhydryl angiotensin-converting enzyme (ACE) inhibitor, which causes decreased aldosterone secretion and increased plasma renin activity.

5.2 Pharmacokinetic properties

Absorption:

When administered orally, enalapril is rapidly absorbed. Approximately

60 % of enalapril is absorbed from oral enalapril maleate, based on urinary recovery. Enalapril is absorbed form the gastrointestinal tract and peak serum concentrations are achieved within one hour.

Enalapril is extensively hydrolysed to enalaprilat in the liver; peak serum concentrations of enalaprilat are achieved 3 - 4 hours after an oral dose of enalapril maleate. In patients with normal renal function, steady state serum concentrations of enalaprilat are achieved by the fourth day of enalapril maleate administration.

The presence of food in the gastrointestinal tract does not influence the absorption of oral enalapril maleate.

Distribution:

Following multiple doses of oral enalapril maleate, the effective half-life of enalaprilat is 11 hours.

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

Biotransformation:

There is no evidence to support the significant metabolism of enalapril, except for the conversion to enalaprilat.

Elimination:

After an oral dose, enalapril is mainly excreted via the urine. The main components in the urine are enalaprilat, about 40 % of the dose, and intact enalapril.

Pharmacokinetics in special patient groups

Renal impairment:

The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatinine clearance 40 - 60 mL/min) steady

state AUC was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤ 30 mL/min), AUC was increased approximately 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed (see section 4.2, Dosage in Renal Insufficiency). Enalaprilat may be removed from the general circulation by haemodialysis.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl cellulose (5 mg tablet only)

Iron oxide red (10 mg and 20 mg tablets only)

Iron oxide yellow (20 mg tablets only)

Lactose monohydrate

Magnesium stearate

Maize starch

Sodium hydrogen carbonate

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place at or below 25 °C.

Keep the blisters in the carton until required for use.

Protect from light.

6.5 Nature and contents of container

Blister strips of 30 tablets are packed, with a leaflet, in a printed outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF 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)

ENAP 5 mg: A34/7.1.3/0085

ENAP 10 mg: A34/7.1.3/0086

ENAP 20 mg: A34/7.1.3/0087

9. DATE OF FIRST AUTHORISATION

30 November 2000

10. DATE OF REVISION OF THE TEXT

15 September 2023

NAMIBIA:

ENAP 5 mg: NS2 04/7.1.3/1138

ENAP 10 mg: NS2 04/7.1.3/1137

ENAP 20 mg: NS2 04/7.1.3/1136

BOSTWANA:

ENAP 5 mg: BOT S2 0701085

ENAP 10 mg: BOT S2 0801495

ENAP 20 mg: BOT S2 0701086

MOZAMBIQUE:

ENAP 5 mg: 4273

ENAP 10 mg: 4274

ENAP 20 mg: 4275