SCHEDULING STATUS: **S3**

1. NAME OF THE MEDICINE.

ENALAPRIL 2,5 mg UNIMED (Tablets)

ENALAPRIL 5 mg UNIMED (Tablets)

ENALAPRIL 10 mg UNIMED (Tablets)

ENALAPRIL 20 mg UNIMED (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSTION

Each **ENALAPRIL 2,5 mg UNIMED** tablet contains 0,5 mg enalapril maleate.

Each **ENALAPRIL 5 mg UNIMED** tablet contains 1,1 mg enalapril maleate.

Each **ENALAPRIL 10 mg UNIMED** tablet contains 2,2 mg enalapril maleate.

Each **ENALAPRIL 20 mg UNIMED** tablet contains 4,3 mg enalapril maleate.

Contains lactose monohydrate

Each **ENALAPRIL 2,5 mg UNIMED** tablet contains 73,17 mg lactose monohydrate.

Each **ENALAPRIL 5 mg UNIMED** tablet contains 146,3 mg lactose monohydrate.

Each **ENALAPRIL 10 mg UNIMED** tablet contains 139,7 mg lactose monohydrate.

Each **ENALAPRIL 20 mg UNIMED** tablet contains 128,9 mg lactose monohydrate.

Contains sodium

Each **ENALAPRIL 2,5 mg UNIMED** tablet contains 0,5 mg of sodium per tablet.

Each **ENALAPRIL 5 mg UNIMED** tablet contains 1,1 mg of sodium per tablet.

Each **ENALAPRIL 10 mg UNIMED** tablet contains 2,2 mg of sodium per tablet.

Each **ENALAPRIL 20 mg UNIMED** tablet contains 4,3 mg of sodium per tablet.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Tablets.

ENALAPRIL 2,5 MG UNIMED:

White, round, biconvex tablet, plain on both sides, 6 mm in diameter.

ENALAPRIL 5 MG UNIMED:

White, oval, biconvex tablets, plain on both sides, 11 mm long and 6 mm wide.

ENALAPRIL 10 mg UNIMED:

Rusty red, oval, biconvex tablets, plain on both sides, 11 mm long and 6 mm wide.

ENALAPRIL 20 mg UNIMED:

Peach, oval, biconvex tablets, plain on both sides, 11 mm long and 6 mm wide.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENALAPRIL UNIMED is indicated in:

Hypertension:

All degrees of essential hypertension. Renovascular hypertension.

Heart failure:

Enalapril maleate can improve existing symptoms and prognosis and diminish the mortality rate and need for hospitalisation, generally with non-potassium-sparing diuretics for heart failure and digitalis for severe heart failure. (section 5.1)

Asymptomatic Left Ventricular Dysfunction:

In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤ 35 %) enalapril maleate decreases the rate of development of overt heart failure and decreases the incidence of hospitalisation for heart failure (see section 5.1)

4.2 Posology and method of administration

Posology

Essential hypertension:

The usual initial dose for mild hypertension is 10 mg once daily. For other degrees of hypertension, 20 mg once a day is recommended. If required, the dosage may be increased gradually over a period of 2 to 4 weeks (or quicker if symptoms so require) to a maintenance dose adjusted according to the needs of the patient. The usual maintenance dose is one 20 mg tablet daily.

Renovascular hypertension:

Therapy should be initiated with a lower starting dose (e.g., 5 mg or less) once a day and then be adjusted according to the needs of the patient. Most patients usually respond to one 20 mg tablet, once daily. Caution is recommended for patients recently treated with diuretics.

Asymptomatic left ventricular dysfunction:

Therapy should be under close medical supervision to determine the initial effect on blood pressure. The usual initial dose is 2,5 mg once a day, increased gradually over 2 to 4 weeks following management of any symptomatic hypotension, to a daily maintenance dose of usually 20 mg either once a day or in two divided doses as required by the patient response. Initiation of preventative treatment may be considered straightforward for patients with a history of myocardial infarction and whose cardiac function tests have been shown to necessitate it; in other cases, systolic left ventricular dysfunction ought to be shown, e.g., by echocardiography or equivalent technique.

Heart failure:

(Co-administration with non-potassium-sparing diuretic or digitalis).

Therapy should be started under close medical supervision or (for severe heart failure) in hospital. The usual initial dose is 2,5 mg once a day, increased gradually over a period of 2 to 4 weeks (or quicker, if signs and symptoms of heart failure are present) to the daily maintenance dose of usually 20 mg either once a day or in two divided doses.

Hypotension and consequent renal failure have been reported following initiation of therapy.

If hypotension is caused by the initial dose and is managed appropriately it need not necessitate cessation of enalapril maleate therapy. If it cannot be managed and becomes symptomatic, revision of the therapeutic regimen is required.

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

Concomitant Therapy:

Dosage adjustment of additional antihypertensive agents in the therapeutic regimen may be necessary. Gradual reduction of the dosage of any beta-blocker in the therapeutic regimen is required, as the dosage of enalapril is titrated up.

There is an increased likelihood of hypotension when enalapril is added to current diuretic therapy. If it is possible, the dose of the diuretic should be decreased or discontinued 2-3 days prior to the start of enalapril therapy, especially as these patients may be volume or salt depleted. If this is not possible, the initial dose of **ENALAPRIL UNIMED** should be low (5 mg or less) to determine the initial effect on the blood pressure. Dosage should then be adjusted according to patient needs.

Special populations

Dosage in Renal Insufficiency:

The minimum maintenance dose that controls symptoms is desirable.

Renal Status	Creatinine Clearance (ml/min)	Initial Dose (mg/day)
Mild impairment	< 80 > 30	5
Moderate impairment	≤ 30 > 10	2,5
Severe impairment (dialysis patients) +	≤ 10	2,5 mg on dialysis days ++

\+ See **4.4 Special warnings and precautions for use.**

++ Enalapril maleate is dialysable; haemodialysis patients may receive the normal dose on the day of dialysis treatment.

Method of administration

Oral use.

ENALAPRIL UNIMED may be taken at any time irrespective of meals, as its absorption is not affected by food.

4.3 Contraindications

Enalapril maleate tablets are contra-indicated in patients who are hypersensitive to the medicine or any of the excipients in the tablets.

Enalapril tablets are also contra-indicated in patients who have:

- had previous treatment with an ACE inhibitor or an angiotensin receptor blocker (ARB) that resulted in angioneurotic oedema. 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
- porphyria
- lithium therapy: Concomitant administration with **ENALAPRIL UNIMED** may lead to toxic blood concentration of lithium.
- Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving an ACE inhibitor, the treatment must be stopped promptly and the patient switched to a different medicine. Should a woman contemplate pregnancy, the doctor should institute alternative medication. (see section 4.2 and 4.6).

- ACE-inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the 2nd and 3rd trimesters. ACE-inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydraminosis, which may result in limb contractures, craniofacial deformities and hypoplastic lung development, as well as hypotension, hyperkalaemia, oliguria and anuria in newborns, have been reported after administration of ACE-inhibitors in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.

Infants whose mothers have taken **ENALAPRIL UNIMED** should be closely observed for hypotension, oliguria and hyperkalaemia. These adverse effects to the embryo and foetus, do not appear to have resulted from intra-uterine ACE-inhibitor exposure, limited to the first trimester.

Enalapril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit.

Symptomatic Hypotension:

- In some uncomplicated hypertensive patients receiving **ENALAPRIL UNIMED,** 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 section 4.5 and 4.8).
- Symptomatic hypotension has been observed in patients with heart failure, who may also have associated renal insufficiency. 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.
- An excessive fall in blood pressure in ischaemic heart or cerebrovascular diseased patients could result in myocardial infarction or cerebrovascular accident. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of **ENALAPRIL UNIMED** and/or diuretic is adjusted.
- 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 congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with **ENALAPRIL UNIMED.**

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 UNIMED** may be necessary.

Renal function Impairment:

- Renal insufficiency results in decreased dose requirements. (see sections 4.2 and 4.3). In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and serum creatinine, reversible upon discontinuation of therapy, have been seen. (see section 4.3). This is especially likely in patients with renal insufficiency. Some patients with no apparent pre-existing renal disease have developed minor and usually transient increases in blood urea and serum creatinine when **ENALAPRIL UNIMED** has been given concomitantly with a diuretic. Dosage reduction of **ENALAPRIL UNIMED** and/or discontinuation of the diuretic may be required.

Hypersensitivity/Angioneurotic Oedema:

- Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported in patients treated with angiotensin-converting enzyme inhibitors, including **ENALAPRIL UNIMED**. In such cases, **ENALAPRIL UNIMED** should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips, the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
- Angioneurotic oedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy such as subcutaneous adrenaline (epinephrine) solution 1:1 000 (0,3 ml to 0,5 ml) should be administered promptly. The patient should be under close

medical supervision until complete and sustained resolution of symptoms has occurred. **These patients should never receive any ENALAPRIL UNIMED or any other ACE inhibitor or angiotensin receptor blockers again.**

- 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)

Anaphylactoid reactions during Hymenoptera Desensitisation:

- Rarely, 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.

Haemodialysis Patients:

- Anaphylactoid reactions have been reported in patients exposed to high-flux membranes dialysis (e.g., AN 69®) or low-density lipoprotein apheresis with dextran sulfate while treated concomitantly with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or methods of LDL apheresis; or a different class of antihypertensive agent.

Cough:

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

Surgery/Anaesthesia:

- In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril maleate 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.

- Severe autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma: Increased risk for development of neutropenia or agranulocytosis.
- 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 UNIMED** 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 UNIMED** 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.
- In acute myocardial infarction, treatment with **ENALAPRIL UNIMED** 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 UNIMED** may need to be withdrawn (see section 4.3).
- Hypotension in acute myocardial infarction-treatment with **ENALAPRIL UNIMED** 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 100 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 to 5 mg or

temporarily to 2,5 mg if systolic blood pressure is 100 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg for more than 1 hour) then **ENALAPRIL UNIMED** should be withdrawn.

- Bone marrow depression – Increased risk of agranulocytosis and neutropenia.
- Diabetes mellitus – Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.
- Hyperkalaemia **–ENALAPRIL UNIMED** may cause an increase in serum potassium levels
- **ENALAPRIL UNIMED** causes a higher rate of angioedema in black patients than in non-black patients.
- Concomitant therapy with potassium sparing diuretics such as spironolatone, triamterene, amiloride may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysrhythmias and cardiac arrest. (see section 4.5).
- 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 UNIMED and** aliskiren is therefore contraindicated (see section 4.3). **ENALAPRIL UNIMED should** not be used concomitantly with aliskiren. (see section 4.3).
- 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

- **ENALAPRIL UNIMED** contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **ENALAPRIL UNIMED.**

- **ENALAPRIL 2,5 mg/ 5 mg/ 10 mg/ 20 mg UNIMED** contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Paediatric population

There is limited documentation of use in children. Use of enalapril in children is not recommended since safety and efficacy has not been completely established.

4.5 Interaction with other medicines and other forms of interaction

Antihypertensive Therapy:

- The combination of **ENALAPRIL UNIMED** with other antihypertensive medicines, may increase the antihypertensive effect, especially in combination with diuretics. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.
- The combination of **ENALAPRIL UNIMED** with beta-adrenergic blocking agents and methyldopa or calcium entry blockers may potentiate the hypotensive effects of **ENALAPRIL UNIMED**.
- Ganglionic blocking agents or adrenergic blocking agents, combined with **ENALAPRIL UNIMED**, should be administered with careful observation of the patient.
- Because of lack of experience, concomitant treatment of **ENALAPRIL UNIMED** with calcium antagonists is not recommended.

Serum Potassium:

- Risk factors for the development of hyperkalaemia of **ENALAPRIL UNIMED** include renal insufficiency, diabetes mellitus and concomitant use of potassium-sparing diuretics, potassium supplements, or potassium-containing salt substitutes.

  In patients with renal failure, the administration of **ENALAPRIL UNIMED m**ay lead to elevation of serum potassium. The use of potassium supplements, potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Serum Lithium:

- Lithium elimination may be reduced. Therefore, the serum lithium levels should be carefully compared if lithium salts are to be administered.

Antidiabetics:

- Epidemiological studies have suggested that concomitant administration of ACE inhibitors as in **ENALAPRIL UNIMED** and antidiabetic medicines (insulins, oral hypoglycaemic agents) 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 agents or insulin, glycaemic control should be closely monitored for hypoglycaemia.

Non-steroidal anti-inflammatory agents including Selective Cyclooxygenase-2 Inhibitors:

- Non-steroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) – reduce the antihypertensive effects

of **ENALAPRIL UNIMED**. Blood pressure monitoring should be increased when any NSAID (including a selective COX-2 inhibitor) is added or discontinued in a patient treated with **ENALAPRIL UNIMED.**

In patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs including selective cyclooxgenase-2 inhibitors, the co-administration of **ENALAPRIL UNIMED** may result in a further deterioration of renal function. These effects are usually reversible.

Gold:

- Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor as in **ENALAPRIL UNIMED** therapy including enalapril.

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, 4.4).

Fluoroquinolones:

- Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3). This may lead to renal impairment due to altered renal haemodynamics in particular clinical

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of **ENALAPRIL UNIMED** is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take **ENALAPRIL UNIMED** during pregnancy (see section 4.3). Patients planning pregnancy should be

changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with **ENALAPRIL UNIMED** should be stopped immediately and if appropriate, alternative therapy should be started. Foetal exposure to ACE inhibitors as in **ENALAPRIL UNIMED** 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 UNIMED** 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 UNIMED** 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 mothers:

Caution should be exercised when enalapril is prescribed for lactating mothers as enalapril and enalaprilat are secreted in human milk. Therefore, the use of **ENALAPRIL UNIMED** is not recommended in women breastfeeding their babies (see section 4.3).

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with Enalapril Maleate.

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	Anaemia (including aplastic and haemolytic), neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, and lymphadenopathy, autoimmune diseases
Endocrine disorders	Not known	Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
	Frequent	Hyperkalaemia.
	Less frequent	Hypoglycaemia including cases of hypoglycaemia in diabetic patients on oral antidiabetic medicine or insulin, hyponatraemia.
Psychiatric disorders	Frequent	Depression.
	Less frequent	Confusion, insomnia, nervousness, dream abnormality, sleep disorders.
Nervous system	Frequent	Dizziness, headache.

		syncope, taste alteration.
	Less frequent	Somnolence, paraesthesia, vertigo.
Eye disorders	Frequent	Blurred vision.
Ear and labyrinth disorders	Less frequent	Tinnitus.
Cardiac disorders	Frequent	Chest pain, rhythm disturbances, angina pectoris, tachycardia, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients.
	Less frequent	Palpitation.
Vascular disorders	Less frequent	Hypotension (including orthostatic hypotension).
	Frequency unknown	Flushing, orthostatic hypotension, Raynaud's phenomenon.
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, dyspnoea.
	Less frequent	Rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma, pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia.
Gastrointestinal disorders	Less frequent	Nausea, diarrhoea, abdominal pain.
	Frequent	Ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritation, dry mouth, peptic ulcer, stomatitis/aphthous ulcerations, glossitis, and intestinal angioedema.
Hepatobiliary disorders	Less frequent	Hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice).
Skin and subcutaneous tissue disorders	Frequent	Rash, hypersensitivity/ angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx.
	Less frequent	Diaphoresis, pruritus, urticaria, alopecia, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus,

		erythroderma.
	Not known	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, flushing, photo sensitivity or other dermatologic manifestations may occur.
Musculoskeletal and connective tissue 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, gynaecomastia.
General disorders and administration site conditions	Frequent	Asthenia, fatigue.
	Less frequent	Malaise, fever.
Investigations	Frequent	increases in serum creatinine.
	Less frequent	Increases in blood urea, elevations of liver enzymes, elevations of serum bilirubin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **ENALAPRIL UNIMED** is important. It allows continued monitoring of the benefit/risk balance of **ENALAPRIL UNIMED**. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Limited data are available for overdosage in humans.

Symptoms

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

Treatment

Treatment is symptomatic and supportive. If ingestion is recent, induce emesis. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume expansion by intravenous infusion of 0,9 % sodium chloride solution to correct hypotension and treating dehydration and electrolyte imbalances. Enalapril maleate may be removed from the general circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 7.1.3 Vascular medicines - other hypotensives

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors

ATC Code: C09A A02

Enalapril maleate is a pro-drug for enalaprilat – a long-acting angiotensin-converting enzyme (ACE) inhibitor. Subsequent to oral absorption, **ENALAPRIL UNIMED** is hydrolysed to enalaprilat. The essential effect of enalaprilat on the renin-angiotensin system is to inhibit the conversion of the inactive angiotensin I to the active angiotensin II. The principal pharmacological and clinical effects of ACE inhibitors arise from the fact that the synthesis of

angiotensin II is suppressed. The consequent inhibition of ACE by enalaprilat causes peripheral vasodilation and fall in blood pressure.

Clinical Pharmacology:

Heart failure, Mortality Trials:

In a multicentre, placebo-controlled trial, 2 569 patients with all degrees of symptomatic heart failure and ejection fraction ≤ 35 %, were randomised to a placebo or enalapril and followed for up to 55 months (SOLVD-Treatment). Use of enalapril was associated with an 11 % reduction in all-cause mortality and a 30 % reduction in hospitalisation for heart failure.

Diseases that excluded patients from enrolment in the study included severe stable angina (> 2 attacks per day), haemodynamically significant valvular or outflow tract obstruction, renal failure (creatinine > 2,5 mg/dl), cerebral vascular disease (e.g., significant carotid artery disease), advanced pulmonary disease, malignancies, active myocarditis and constructive pericarditis. The mortality benefit associated with enalapril does not appear to depend on digitalis being present.

A second multicentre trial used the SOLVD protocol for a study of asymptomatic or minimally symptomatic patients. SOLVD-Prevention patients, who had left ventricular ejection fraction ≤ 35 % and no history of symptomatic heart failure were randomised to placebo (n = 2 117) or enalapril (n = 2 111) and followed for up to 5 years. The majority of patients in the SOLVD-Prevention trial had a history of ischaemic heart disease. A history of myocardial infarction was present in 80 percent of patients, current angina pectoris in 34 percent, and a history of hypertension in 37 percent. No statistically significant mortality effect was demonstrated in this population. Enalapril-treated subjects had 32 percent fewer first hospitalisations for heart failure and 32 percent fewer total heart failure hospitalisations.

Compared to placebo, 32 percent fewer patients receiving enalapril developed symptoms of overt heart failure. Hospitalisations for cardiovascular reasons were also reduced. There was an insignificant reduction in hospitalisations for any cause in the enalapril treatment group (for enalapril vs. placebo, respectively, 1 166 vs. 12 01 first hospitalisations, 2 649 vs. 2 840 total hospitalisations), although the study was not powered to look for such an effect. The SOLVD-Prevention trial was not designed to determine whether treatment of asymptomatic patients with low ejection fraction would be superior, with respect to preventing hospitalisations, to closer follow-up and use of enalapril at the earlier sign of heart failure. However, under the conditions of follow up in the SOLVD-Prevention trial (every 4 months at the study clinic, personal physician as needed), 68 % of patients on placebo who were hospitalised for heart failure had no prior symptoms recorded which would have signalled initiation of treatment.

The SOLVD-Prevention trial was also not designed to show whether enalapril modified the progression of underlying heart disease.

In another multicentre, placebo-controlled trial (CONSENSUS), limited to patients with NYHA Class IV congestive heart failure and radiographic evidence of cardiomegaly, use of enalapril was associated with improved survival. The results are shown in the following table.

	Survival (%) Six months	One year
Renitec (n=127)	74	64
Placebo (n = 126)	56	48

In both the CONSENSUS and SOLVD-Treatment trials, patients were also receiving digitalis, diuretics or both.

Long-term enalapril therapy has benefited symptomatic and asymptomatic heart failure patients by the reduction of overall mortality, a greater reduction of potential subsequent hospitalisation and fewer patients developing symptoms of overt heart failure.

5.2 Pharmacokinetic properties

Following oral administration, enalapril maleate is rapidly absorbed, unaffected by food. Hydrolysis to the active form, enalaprilat, takes place and peak enalaprilat levels are attained in 3 to 4 hours.

Plasma protein binding is 50 – 60 %. Pharmacological activity increases gradually after administration and continues for up to 24 hours.

Absorption

Enalapril is absorbed from the gastro-intestinal tract and has an oral bio-availability of approximately 60 %. The absorption of oral enalapril is not influenced by the presence of food in the gastrointestinal tract.

Distribution

Peak plasma of enalapril occur within an hour and it has a plasma half-life of approximately 1,3 hours, while the active form, enalaprilat, only peaks after 3- 4 hours and has a plasma half-life of up to 11 hours. Enalaprilat is 50-60 % bound to plasma proteins.

Biotransformation

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

Elimination

Elimination is mainly via the kidneys (60 %) as intact enalapril and enalaprilat accounting for about 40 % of the dose. The remainder is eliminated in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ENALAPRIL 2,5 & 5 mg UNIMED

Starch Pregelatinized

Maize starch

Sodium bicarbonate

Lactose monohydrate

Magnesium stearate

ENALAPRIL 10 & 20 mg UNIMED

Starch Pregelatinized

Maize starch

Sodium bicarbonate

Lactose monohydrate

Ferric Oxide

Magnesium stearate

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 ºC. Protect from light.

Keep the blisters in the cartons until required for use.

Keep the securitainers well-closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack of 10, 14, 28 or 30 tablets of each strength.

High density polyethylene container or amber glass bottle of 30, 50, 56, 100

or 500 tablets of each strength.

6.6 Special precautions for disposal

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue

Anchorville

Lenasia

1827

South Africa

8. REGISTRATION NUMBERS

ENALAPRIL 2,5 mg UNIMED:35/7.1.3/0051

ENALAPRIL 5 mg UNIMED:35/7.1.3/0052

ENALAPRIL 10 mg UNIMED:35/7.1.3/0053

ENALAPRIL 20 mg UNIMED:35/7.1.3/0054

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 November 2002

10. DATE OF REVISION OF THE TEXT

21 June 2024