SCHEDULING STATUS: **S3**

PROPRIETARY NAME (and dosage form):

ENALAPRIL 2,5 mg UNIMED (Tablets)

ENALAPRIL 5 mg UNIMED (Tablets)

ENALAPRIL 10 mg UNIMED (Tablets)

ENALAPRIL 20 mg UNIMED (Tablets)

COMPOSITION:

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

Contains sugar: Lactose monohydrate 73,17 mg/tablet.

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

Contains sugar: Lactose monohydrate 146,3 mg/tablet.

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

Contains sugar: Lactose monohydrate 140,2 mg/tablet.

Each **ENALAPRIL 20 mg UNIMED** tablet contains 20 mg enalapril maleate.

Contains sugar: Lactose monohydrate 128,9 mg/tablet.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Vascular medicines – other hypotensives

PHARMACOLOGICAL ACTION:

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 consequent inhibition of ACE by enalaprilat causes peripheral vasodilation and fall in blood pressure.

Clinical Pharmacology:

Heart failure, Mortality Rates:

In a multicentre, placebo-controlled trial, 2 569 patients with all degrees of symptomatic heart failure and ejection fraction ≤ 35 percent, were randomised to a placebo or enalapril and followed for up to 55 months (SOLVD-Treatment). Use of enalapril was associated with an 11 percent reduction in all-cause mortality and a 30 percent 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 percent and no history of symptomatic heart failure were randomised to placebo (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. 1 201 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 benefitted 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.

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.

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. (See "**Clinical Pharmacology: Heart Failure, Mortality Rates**" under "**PHARMACOLOGICAL ACTION**" for details).

Asymptomatic Left Ventricular Dysfunction:

In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction ≤ 35 percent) enalapril maleate decreases the rate of development of overt heart failure and decreases the incidence of hospitalisation for heart failure (See "**Clinical Pharmacology: Heart Failure, Mortality Rates**" under "**PHARMACOLOGICAL ACTION**" for details).

CONTRA-INDICATIONS:

Enalapril maleate tablets are contra-indicated in patients who are hypersensitive to the drug 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 that resulted in angioneurotic oedema.

Nursing mothers:

Caution should be exercised when enalapril is prescribed for lactating mothers as enalapril and enalaprilat are secreted in human milk.

Use in children:

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.

WARNINGS:

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.

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

DOSAGE AND DIRECTION FOR USE:

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

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 should be increased gradually over a period of 2 to 4 weeks (or quicker if symptoms so require) to a maintenance dose 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 blood pressure effect. 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 "**INTERACTIONS"**).

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.

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 "**SPECIAL PRECAUTIONS".**

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

The most common side effects are dizziness and headache. Less frequently reported side-effects include asthenia, cough, diarrhoea, fatigue, hypotension, muscle cramps, nausea, orthostatic hypotension, rash and syncope. To a lesser extent, renal dysfunction, renal failure and oliguria have been reported.

Hypersensitivity/Angioneurotic Oedema:

Angioneurotic oedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx have been reported. (See "**SPECIAL PRECAUTIONS**").

Cardiovascular:

Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (See "**SPECIAL PRECAUTIONS**"). Chest pain, palpitations rhythm disturbances, angina pectoris.

Gastrointestinal:

Range from abdominal pain, vomiting, dyspepsia and constipation to pancreatitis, hepatic failure, ileus, hepatitis - either hepatocellular or cholestatic, jaundice, anorexia and stomatitis.

Nervous System/Psychiatric:

Depression, insomnia, somnolence, confusion, nervousness, vertigo and paraesthesiae have been reported.

Respiratory:

In addition to the persistent non-productive cough (that resolves when therapy is discontinued) reported with ACE-inhibitors, rare respiratory side-effects include bronchospasm, asthma, dyspnoea, rhinorrhoea, sore throat, hoarseness and pulmonary infiltrates.

Skin:

Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus, pruritus, urticaria, flushing and alopecia, diaphoresis, erythema multiforme, exfoliative dermatitis.

Other:

Impotence, taste alteration, tinnitus, glossitis, blurred vision.

A symptom complex has been reported which may include fever, serositis, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibody, elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Clinical Laboratory Test Findings:

Increases in blood urea and serum creatinine, and elevations of liver enzymes and/or serum bilirubin have been seen. These are usually reversible upon discontinuation of **ENALAPRIL UNIMED** treatment. Hyperkalaemia and hyponatraemia have occurred. Decreases in haemoglobin and haematocrit have been reported.

SPECIAL PRECAUTIONS:

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 "**INTERACTIONS"** and "**SIDE-EFFECTS"**). 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 table above **- Dosage in Renal Insufficiency.**) 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. 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 epinephrine solution 1:1 000 (0,3 ml to 0,5 ml) should be administered promptly.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE-inhibitor. (Also see "**CONTRA-INDICATIONS"**).

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 dialysed with high-flux membranes (e.g. AN 69®) and treated concomitantly with an ACE-inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive 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.

Serum Potassium – See "**INTERACTIONS"**.

Paediatric Use:

See **"CONTRA-INDICATIONS"**.

MEDICINE INTERACTIONS:

Antihypertensive Therapy:

The combination of **ENALAPRIL UNIMED** with other antihypertensive medicines, may increase the antihypertensive effect, especially in combination with diuretics.

The combination of **ENALAPRIL UNIMED** with beta-adrenergic blocking agents and methyldopa or calcium entry blockers may increase the antihypertensive effect.

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** may 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:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Limited data are available for overdosage in humans. 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, and stupor.
The recommended treatment of overdosage is intravenous infusion of normal saline solution.
If ingestion is recent, induce emesis.
Enalapril maleate may be removed from the general circulation by haemodialysis.

IDENTIFICATION:

ENALAPRIL 2,5 mg UNIMED:

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

ENALAPRIL 5 mg UNIMED:

White, oval, biconvex tablet, plain on both sides, 11,0 mm long and 6 mm wide.

ENALAPRIL 10 mg UNIMED:

Rusty red, oval, biconvex tablets, plain on both sides, 11,0 mm long and 6 mm wide.

ENALAPRIL 20 mg UNIMED:

Peach, oval, biconvex tablets, plain on both sides,11,0 mm long and 6 mm wide.

PRESENTATION:

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.

STORAGE INSTRUCTIONS:

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

Keep the blisters in the carton until required for use.

Keep the HDPE container or glass bottle well-closed.

KEEP OUT OF REACH OF CHILDREN.

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

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