Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Enapril Stada 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20mg of enalapril maleate.

Excipients: Contains Lactose Monohydrate 117.8mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Round, convex 'snap tab' tablets, scored on one side pale orange in colour with individual white spots.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Treatment of Hypertension.
- Treatment of Symptomatic Heart Failure.
- Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤ 35%).

4.2 Posology and method of administration

The absorption of Enapril Stada 2.5mg/5mg/10mg/20mg tablets is not affected by food.
The dose should be individualized according to patient profile (see 4.4 Special warnings and special precautions for use) and blood pressure response.

Hypertension
The initial dose is 5 to maximally 20 mg, depending on the degree of hypertension and the condition of the patient (see below). Enapril Stada 2.5mg/5mg/10mg/20mg tablets are given once daily. In mild hypertension, the recommended initial dose is 5 to 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (e.g., renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 5 mg or lower is recommended in such patients and the initiation of treatment should take place under medical supervision.

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enapril. A starting dose of 5 mg or lower is recommended in such patients. If possible, diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Enapril Stada 2.5mg/5mg/10mg/20mg tablets. Renal function and serum potassium should be monitored.
The usual maintenance dose is 20 mg daily. The maximum maintenance dose is 40 mg daily.

Heart Failure/Asymptomatic Left Ventricular Dysfunction
In the management of symptomatic heart failure, Enapril Stada 2.5mg/5mg/10mg/20mg tablets is used in addition to diuretics and, where appropriate, digitalis or beta-blockers. The initial dose of Enapril Stada 2.5mg/5mg/10mg/20mg tablets in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with Enapril Stada 2.5mg/5mg/10mg/20mg tablets in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient. This dose titration is recommended to be performed over a 2 to 4 week period. The maximum dose is 40 mg daily given in two divided doses.

Suggested Dosage Titration of Enapril Stada 2.5mg/5mg/10mg/20mg tablets in Patients with Heart Failure/Asymptomatic Left Ventricular Dysfunction.

Week	**Dose mg/day**
Week 1	**Days 1 to 3:** 2.5 mg/day* in a single dose **Days 4 to 7:** 5 mg/day in two divided doses
Week 2	10 mg/day in a single dose or in two divided doses
Weeks 3 and 4	20 mg/day in a single dose or in two divided doses

*Special precautions should be followed in patients with impaired renal function or taking diuretics (See 4.4 Special warnings and special precautions for use).

Blood pressure and renal function should be monitored closely both before and after starting treatment with Enapril Stada 2.5mg/5mg/10mg/20mg tablets (see 4.4 Special warnings and special precautions for use) because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics, the dose should be reduced if possible before beginning treatment with Enapril Stada 2.5mg/5mg/10mg/20mg tablets. The appearance of hypotension after the initial dose of Enapril Stada 2.5mg/5mg/10mg/20mg tablets does not imply that hypotension will recur during chronic therapy with Enapril Stada 2.5mg/5mg/10mg/20mg tablets and does not preclude continued use of the drug. Serum potassium and renal function also should be monitored.

Dosage in Renal Insufficiency
Generally, the intervals between the administration of Enapril should be prolonged and/or the dosage reduced.

Creatinine Clearance (CrCL)	**Initial Dose**
mL/min	**mg/day**
30<CrCL<80 ml/min	5 - 10 mg
10<CrCL≤30 ml/min.	2.5 mg
CrCL≤10 ml/min.	2.5 mg on dialysis days*

*See 4.4 Special warnings and special precautions for use - Hemodialysis Patients. Enapril at is dialyzable. Dosage on nondialysis days should be adjusted depending on the blood pressure response.

Use in Elderly
The dose should be in line with the renal function of the elderly patient (see 4.4 Special warnings and special precautions for use, Renal Function Impairment).

Use in paediatrics
There is limited clinical trial experience of the use of Enapril Stada 2.5mg/5mg/10mg/20mg tablets in hypertensive

paediatric patients (see 4.4 Special warnings and special precautions for use, 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties).
For patients who can swallow tablets, the dose should be individualized according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥50 kg. Enapril Stada 2.5mg/5mg/10mg/20mg tablets is given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients ≥50 kg. (See 4.4 Special warnings and special precautions for use.)
Enapril Stada 2.5mg/5mg/10mg/20mg tablets are not recommended in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2, as no data are available.

Instruction for use
Place the Enapril Stada 5mg/10mg/20mg snaptab tablet on a hard surface with the centre groove facing upward. Exert pressure from the top with your thumb and the snaptab will break into two equal pieces.

4.3 Contraindications

- Hypersensitivity to Enalapril, to any of the excipients or any other ACE inhibitor
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Symptomatic Hypotension
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving Enapril Stada 2.5mg/5mg/10mg/20mg tablets, symptomatic hypotension is more likely to occur if the patient has been volume - depleted, e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting (see 4.5 Interaction with other medicaments and other forms of interaction and 4.8 Undesirable Effects). 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 Enapril Stada 2.5mg/5mg/10mg/20mg tablets and/or diuretic is adjusted. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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 contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Enapril Stada 2.5mg tablets. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or Enapril Stada 2.5mg/5mg/10mg/20mg tablets may be necessary.

Aortic or Mitral Valve Stenosis/Hypertrophic Cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal Function Impairment
In cases of renal impairment (creatinine clearance <80 ml/min) the initial Enalapril dosage should be adjusted according to the patient's creatinine clearance (see 4.2 Posology and method of administration) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.
Renal failure has been reported in association with Enalapril and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognized promptly and treated appropriately, renal failure when associated with therapy with Enalapril is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when Enalapril has been given concurrently with a diuretic. Dosage reduction of Enalapril and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see 4.4 Special warnings and special precautions for use, Renovascular hypertension).

Renovascular hypertension
There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

Kidney Transplantation
There is no experience regarding the administration of Enapril Stada 2.5mg/5mg/10mg/20mg tablets in patients with a recent kidney transplantation. Treatment with Enapril Stada 2.5mg/5mg/10mg/20mg tablets is therefore not recommended.

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

Neutropenia/Agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If Enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity/Angioneurotic Edema
Angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including Enapril Stada 2.5mg/5mg/10mg/20mg tablets. This may occur at any time during treatment. In such cases, Enapril Stada 2.5mg/5mg/10mg/20mg tablets should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.
Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.
Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.
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 4.3 Contraindications.)

Anaphylactoid Reactions during Hymenoptera Desensitization
Rarely, patients receiving ACE inhibitors during desensitization with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitization.

Anaphylactoid Reactions during LDL Apheresis
Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Hemodialysis Patients
Anaphylactoid reactions have been reported in patients dialyzed 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.

Hypoglycemia
Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor, should be told to closely monitor for hypoglycemia, especially during the first month of combined use. (See 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

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

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Enalapril 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.

Hyperkalemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of enalapril and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium. (See 4.5 Interaction with other medicinal products and other forms of interaction.)

Lithium
The combination of lithium and Enalapril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

Lactose
Enapril Stada 2.5mg tablets contains lactose-monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatric Use
There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Limited pharmacokinetic data are available in children above 2 months of age. (Also see 4.2 Posology and method of administration, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties.) Enapril Stada 2.5mg/5mg/10mg/20mg tablets is not recommended in children in other indications than hypertension.
Enapril Stada 2.5mg/5mg/10mg/20mg tablets is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2, as no data are available. (See 4.2 Posology and method of administration.)

Pregnancy and lactation

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Use of enalapril is not recommended during breast feeding (see sections 4.6 and 5.2).

Ethnic differences
As with other angiotensin converting enzyme inhibitors, Enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction

Potassium sparing diuretics or potassium supplements
ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium (see 4.4 Special warnings and special precautions for use).

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with Enalapril (see 4.4 Special warnings and special precautions for use). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of Enalapril.

Other antihypertensive agents
Concomitant use of these agents may increase the hypotensive effects of Enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of Enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see 4.4 Special warnings and special precautions for use).

Tricyclic antidepressants/Antipsychotics/Anesthetics/Narcotics
Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see 4.4 Special warnings and special precautions for use).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor.
NSAIDs (including COX-2 inhibitors) and ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually 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). Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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 therapy including enalapril.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Alcohol
Alcohol enhances the hypotensive effect of ACE inhibitors.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.) Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of Enapril Stada in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of Enapril Stada in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

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

Undesirable effects reported for Enalapril include:

[Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)]

Blood and the lymphatic system disorders:
uncommon: anemia (including aplastic and hemolytic)
rare: neutropenia, decreases in hemoglobin, decreases in hematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases

Endocrine disorders:
not known: syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and nutrition disorders:
uncommon: hypoglycemia (see 4.4 Special warnings and special precautions for use, Diabetic patients)

Nervous system and psychiatric disorders:
common: headache, depression
uncommon: confusion, somnolence, insomnia, nervousness, paresthesia, vertigo
rare: dream abnormality, sleep disorders

Eye disorders:
very common: blurred vision

Cardiac and vascular disorders:
very common: dizziness
common: hypotension (including orthostatic hypotension), syncope, , chest pain, rhythm disturbances, angina pectoris, tachycardia
uncommon: orthostatic hypotension, palpitations myocardial infarction or cerebrovascular accident*, possibly secondary to excessive hypotension in high risk patients (see 4.4 Special warnings and special precautions for use)
rare: Raynaud‘s phenomenon

Respiratory, thoracic and mediastinal disorders:
very common: cough
common: dyspnea uncommon: rhinorrhea, sore throat and hoarseness, bronchospasm/asthma
rare: pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:
very common: nausea
common: diarrhea, abdominal pain, taste alteration
uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer
rare: stomatitis/aphthous ulcerations, glossitis
very rare: intestinal angioedema

Hepatobiliary disorders:
rare: hepatic failure, hepatitis -either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice)

Skin and subcutaneous tissue disorders:
common: rash, hypersensitivity/angioneurotic edema: angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see 4.4 Special warnings and special precautions for use)
uncommon: diaphoresis, pruritus, urticaria, alopecia
rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma

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 leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Renal and urinary disorders:
uncommon: renal dysfunction, renal failure, proteinuria
rare: oliguria

Reproductive system and breast disorders:
uncommon: impotence
rare: gynecomastia

General disorders and administration site conditions:
very common: asthenia
common: fatigue uncommon: muscle cramps, flushing, tinnitus, malaise, fever

Investigations:
common: hyperkalemia, increases in serum creatinine
uncommon: increases in blood urea, hyponatremia
rare: elevations of liver enzymes, elevations of serum bilirubin

*Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.

4.9 Overdose

Limited data are available for overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdosage of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum Enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of Enalapril, respectively.
The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If 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, gastric lavage, administration of absorbents, and sodium sulphate). Enalaprilat may be removed from the general circulation by hemodialysis. (See 4.4 Special warnings and special precautions for use, Hemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC Code: C09A A02
Enapril Stada 2.5mg/5mg/10mg/20mg tablets (Enalapril maleate) is the maleate salt of Enalapril, a derivative of two amino-acids, L-alanine and L-proline. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, Enalapril is hydrolyzed to Enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.
ACE is identical to kininase II. Thus Enalapril tablets may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of Enapril Stada 2.5mg/5mg/10mg/20mg tablets remains to be elucidated.
While the mechanism through which Enapril Stada 2.5mg/5mg/10mg/20mg tablets lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, Enapril Stada 2.5mg/5mg/10mg/20mg tablets is antihypertensive even in patients with low-renin hypertension.

Administration of Enapril Stada 2.5mg/5mg/10mg/20mg tablets to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate.
Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of Enalapril tablets has not been associated with rapid increase in blood pressure.
Effective inhibition of ACE activity usually occurs 2 to 4 hours after oral administration of an individual dose of Enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by 4 to 6 hours after administration. The duration of effect is dose-related. However, at recommended doses, antihypertensive and hemodynamic effects have been shown to be maintained for at least 24 hours.
In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate.
Following administration of Enalapril tablets there was an increase in renal blood flow; glomerular filtration rate was unchanged. There was no evidence of sodium or water retention. However, in patients with low pretreatment glomerular filtration rates, the rates were usually increased.
In short term clinical studies in diabetic and nondiabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of Enalapril.
When given together with thiazide-type diuretics, the blood pressure-lowering effects of Enalapril tablets are at least additive. Enalapril tablets may reduce or prevent the development of thiazide-induced hypokalemia.
In patients with heart failure on therapy with digitalis and diuretics, treatment with oral or Injection Enalapril tablets were associated with decreases in peripheral resistance and blood pressure. Cardiac output increased, while heart rate (usually elevated in patients with heart failure) decreased. Pulmonary capillary wedge pressure was also reduced. Exercise tolerance and severity of heart failure, as measured by New York Heart Association criteria, improved. These actions continued during chronic therapy.
In patients with mild to moderate heart failure, Enalapril retarded progressive cardiac dilatation/enlargement and failure, as evidenced by reduced left ventricular end diastolic and systolic volumes and improved ejection fraction.
A multicenter, randomised, double-blind, placebo-controlled trial (SOLVD Prevention trial) examined a population with asymptomatic left ventricular dysfunction (LVEF<35%). 4228 patients were randomized to receive either placebo (n=2117) or Enalapril (n=2111). In the placebo group, 818 patients had heart failure or died (38.6%) as compared with 630 in the Enalapril group (29.8%) (risk reduction: 29%; 95% CI; 21 - 36%; p<0.001). 518 patients in the placebo group (24.5%) and 434 in the Enalapril group (20.6%) died or were hospitalized for new or worsening heart failure (risk reduction 20%; 95% CI; 9 - 30%; p<0.001).
A multicenter, randomised, double-blind, placebo-controlled trial (SOLVD Treatment trial) examined a population with symptomatic congestive heart failure due to systolic dysfunction (ejection fraction <35%). 2569 patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo (n=1284) or Enalapril (n=1285). There were 510 deaths in the placebo group (39.7%) as compared with 452 in the Enalapril group (35.2%) (reduction in risk, 16%; 95% CI, 5 26%; p=0.0036). There were 461 cardiovascular deaths in the placebo group as compared with 399 in the Enalapril group (risk reduction 18%, 95% CI, 6 - 28%, p<0.002), mainly due to a decrease of deaths due to progressive heart failure (251 in the placebo group vs 209 in the Enalapril group, risk reduction 22%, 95% CI, 6 - 35%).

Fewer patients died or were hospitalized for worsening heart failure (736 in the placebo group and 613 in the Enalapril group; risk reduction, 26%; 95% CI, 18 - 34%; p<0.0001). Overall in SOLVD study, in patients with left ventricular dysfunction, Enapril Stada 2.5mg/5mg/10mg/20mg tablets reduced the risk of myocardial infarction by 23% (95% CI, 11 - 34%; p<0.001) and reduced the risk of hospitalization for unstable angina pectoris by 20% (95% CI, 9 - 29%; p<0.001).

There is limited experience of the use in hypertensive pediatric patients >6 years. In a clinical study involving 110 hypertensive pediatric patients 6 to 16 years of age with a body weight ≥20 kg and a glomerular filtration rate >30 ml/min/1.73 m^2, patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of Enalapril daily and patients who weighed <50 kg received either 1.25, 5 or 40 mg of Enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of Enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. The maximum dose studied was 0.58 mg/kg (up to 40 mg) once daily. The adverse experience profile for pediatric patients is not different from that seen in adult patients.

5.2 Pharmacokinetic properties

Absorption
Oral Enalapril is rapidly absorbed, with peak serum concentrations of Enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of Enalapril from oral Enalapril tablet is approximately 60%. The absorption of oral Enapril Stada 2.5mg/5mg/10mg/20mg tablets is not influenced by the presence of food in the gastrointestinal tract.

Following absorption, oral Enalapril is rapidly and extensively hydrolyzed to Enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of Enalaprilat occur about 4 hours after an oral dose of Enalapril tablet. The effective half-life for accumulation of Enalaprilat following multiple doses of oral Enalapril is 11 hours. In subjects with normal renal function, steady-state serum concentrations of Enalaprilat were reached after 4 days of treatment.

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%).

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 of Enalaprilat 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 4.2 Posology and method of administration.) Enalaprilat may be removed from the general circulation by hemodialysis.
The dialysis clearance is 62 ml/min.

Children and adolescents
A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged 2 months to ≤16 years following daily oral administration of 0.07 to 0.14 mg/kg Enalapril maleate. There were no major differences in the pharmacokinetics of Enalaprilat in children compared with historic data in adults. The data indicate an increase in AUC (normalised to dose per body weight) with increased age; however, an increase in AUC is not observed when data are normalised by body surface area. At steady state, the mean effective half-life for accumulation of Enalaprilat was 14 hours.

Lactation
After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7µg/L (range 1.2 to 2.3µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weight-adjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 µg/L 4 hours after a dose and peak enalaprilat levels of 0.75 µg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44µg/L and 0.63 µg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies suggest that Enalapril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation. The compound has been shown to cross the placenta and is secreted in milk. Angiotensin converting enzyme inhibitors, as a class, have been shown to be fetotoxic (causing injury and/or death to the fetus) when given in the second or third trimester.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Lactose monohydrate
Maize starch
Talc
Magnesium stearate
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life is 3 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Aluminium/OPA-Al-PVC blister foil

Original pack of
10, 14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
* not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastraße 2-18
61118 Bad Vilbel,
Germany

8 MARKETING AUTHORISATION NUMBER

PA 593/24/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd March 2001
Date of last renewal: 21st March 2010

10 DATE OF REVISION OF THE TEXT

July 2011