C09 AA02

1. NAME OF THE MEDICINAL PRODUCT

Enap 1.25 mg/1 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection (1 ampoule) contains 1.25 mg enalaprilat.

Excipients: benzyl alcohol (9 mg/1 ml), sodium (2.5 mg/1 ml).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
The solution for injection is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Arterial hypertension when oral treatment is not possible.

4.2 Posology and method of administration

The usual dose for the treatment of hypertension is 1 ampoule (1.25 mg) every 6 hours.
When switching from treatment with enalapril to treatment with enalaprilat, the usual dose is 1 ampoule (1.25 mg) every six hours.

Enap solution for injection should be administered slowly intravenously, over at least 5 minutes. It can also be administered diluted in 50 ml of 5% glucose, 0.9% sodium chloride solution (physiological solution), 5% glucose in 0.9% sodium chloride solution, or 5% glucose in Ringer's lactate.

For patients on diuretic therapy, the initial dose is ½ ampoule (0.625 mg). If after one hour there is an inadequate clinical response, the same dose may be repeated and treatment continued with the full dose after 6 hours (1 ampoule every 6 hours).

Treatment with enalaprilat usually lasts for 48 hours. Thereafter, treatment should be continued with enalapril.
When switching from parenteral treatment with enalaprilat to oral treatment with enalapril, the recommended initial dose is 5 mg a day for patients having received 1 ampoule (1.25 mg) of enalaprilat every 6 hours. If necessary, the dose may be increased. For patients initially treated with half the starting dose of enalaprilat (0.625 mg), the recommended dose when switching to oral treatment is 2.5 mg enalapril a day.

Dosage in renal insufficiency
For patients with a creatinine clearance >0.5 ml/s (30 ml/min, serum creatinine of up to 265 µmol/l), the initial dose is 1 ampoule (1.25 mg) every 6 hours.
For patients with a creatinine clearance <0.5 ml/s (30 ml/min, serum creatinine >265 µmol/l), the initial dose is ½ ampoule (0.625 mg). If after one hour there is an inadequate clinical response, the same dose may be repeated and treatment continued with the full dose after 6 hours (1 ampoule every 6 hours).

Dosage in haemodialysis

For haemodialysis patients, the recommended dose is ½ ampoule (0.625 mg) every 6 hours.

Use in children
Due to insufficient data on safety and/or efficacy, the use of enalaprilat in children is not recommended.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Symptomatic hypotension
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. It is more likely to occur in hypertensive patients who have been volume depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see sections 4.5 and 4.8). Symptomatic hypotension may occur in patients with heart failure, with or without associated renal insufficiency. This is more 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 renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of enalapril and/or diuretic is adjusted. Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
Hypotension and its severe consequences are rare and transient. They can be avoided by discontinuing treatment with diuretics and low-salt diet prior to initiating treatment with Enap, if possible. In other mentioned conditions or if the diuretic treatment cannot be discontinued, it is recommended to institute treatment with half the dose (½ ampoule) of enalaprilat.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride solution to expand the plasma volume. Transient hypotension is not a contraindication to treatment with enalapril. After blood pressure and plasma volume are corrected, patients usually tolerate further doses well.

Aortic or mitral valve stenosis/hypertrophic cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with special caution in patients with left ventricular outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant left ventricular outflow tract obstruction.

Renal function impairment
In patients with renal impairment (creatinine clearance <1.33 ml/s), the dose should be adjusted according to the creatinine clearance (see section 4.2) and then according to the response to treatment. Serum creatinine and potassium levels should be monitored regularly.
In patients with severe heart failure or underlying renal disease, including renal artery stenosis, renal failure may occur during treatment with enalapril. If recognised promptly and treated appropriately, it is usually reversible.
Some patients with no apparent pre-existing renal disease have developed minor and transient increases in serum urea and creatinine levels when enalapril has been given concurrently with a diuretic. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see section 4.4).

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 medical supervision with low doses; careful titration and monitoring of renal function during treatment are required.

Kidney transplantation
There is no experience regarding the administration of enalapril in patients with a recent kidney transplantation. Treatment with enalapril is therefore not recommended.

Hepatic failure
During treatment with ACE inhibitors, a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death may rarely occur. The mechanism of this syndrome is not understood. If jaundice or marked elevations of hepatic enzymes occur during treatment with an ACE inhibitor, treatment should be discontinued immediately, the patient monitored closely and treated, if necessary.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complications, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease (e.g. systemic lupus erythematosus, scleroderma), concomitant immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these factors, especially if there is pre-existing impaired renal function. Some of these patients may develop serious infections, which sometimes do not respond to intensive antibiotic therapy. If enalapril/enalaprilat is used in such patients, periodic monitoring of white blood cell counts is advised. Patients should be instructed to report any sign of infection.

Hypersensitivity/angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs rarely during treatment with ACE inhibitors, including enalapril or enalaprilat. This may occur at any time during treatment. In such cases, treatment should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms.
Angioedema of the face and lips usually does not require treatment; antihistamines can be used to relieve the patient's symptoms.
Angioedema of the larynx may be fatal. In angioedema of the tongue, glottis or larynx, which may cause airway obstruction, adrenaline (0.3 ml to 0.5 ml of subcutaneous adrenaline solution at a ratio of 1:1000) should be administered immediately and a patent airway ensured.
Patients with a history of angioedema unrelated to ACE inhibitor therapy are at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Anaphylactoid reactions during desensitisation
Patients receiving ACE inhibitors during desensitisation with wasp or bee venom may rarely experience life-threatening, allergy-like (anaphylactoid) reactions. These reactions can be avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

Anaphylactoid reactions during LDL apheresis
Patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate may rarely experience life-threatening, allergy-like (anaphylactoid) reactions. These reactions can be avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Haemodialysis patients
Hypersensitivity, allergy-like (anaphylactoid) reactions have been reported in patients dialysed with high-flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. If haemodialysis is required, the patient should first be switched to a drug of a different class, or a different type of dialysis membrane should be used.

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, blood sugar levels should be closely monitored during the first few months of concomitant treatment with ACE inhibitors (see section 4.5).

Cough
Persistent, dry, non-productive cough, which resolves after discontinuation of therapy, may occur during treatment with ACE inhibitors. It 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 may block 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.

Hyperkalaemia
During treatment with ACE inhibitors, including enalapril and enalaprilat, blood potassium levels may increase in some patients. The risk of hyperkalaemia is greater in patients with renal insufficiency, diabetes, in those using concomitant potassium-sparing diuretics, potassium supplements or other drugs that may cause hyperkalaemia (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Lithium
The combination of lithium and enalapril is generally not recommended (see section 4.5).

Pregnancy and lactation
Enalapril should not be used during the first trimester of pregnancy and it is contraindicated in the second and third trimesters of pregnancy (see section 4.3). When pregnancy is detected, enalapril treatment should be discontinued as soon as possible (see section 4.6).
Use of enalapril is not recommended during breast-feeding.

Ethnic differences
Like all ACE inhibitors, enalapril is 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.

Special information about some of the ingredients
Enap solution for injection contains benzyl alcohol, which may cause toxic and anaphylactic reactions in infants and children under 3 years of age. It should not be given to premature and newborn infants. This drug contains less than 1 mmol (23 mg) sodium per dose, which means it is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Enalaprilat is a metabolite of enalapril. Therefore, during treatment with enalaprilat, the same interactions may occur as during treatment with enalapril.

Potassium-sparing diuretics, potassium supplements
ACE inhibitors attenuate diuretic-induced potassium loss. Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to hyperkalaemia. If concomitant use is indicated because of demonstrated hypokalaemia, they should be used with great caution and with frequent monitoring of serum potassium (see section 4.4).

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics may result in volume depletion and increase the risk of excessive hypotension (see section 4.4). The hypotensive effect can be reduced by discontinuing the

diuretic, by increasing salt and fluid intake or by initiating therapy with half a dose (½ ampoule) of enalaprilat.

Other antihypertensive agents
Concomitant use of enalapril and another antihypertensive drug may increase the antihypertensive effect of enalapril. Concomitant use with nitroglycerine, other nitrates or other vasodilators may further reduce blood pressure.

Lithium
Transient increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of ACE inhibitors and thiazide diuretics may further increase serum lithium levels and enhance the risk of lithium toxicity. Use of enalapril with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Tricyclic antidepressants/antipsychotics/anaesthetics/narcotics
Concomitant use of certain anaesthetics, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Nonsteroidal anti-inflammatory drugs (NSAIDs)
Chronic administration of NSAIDs may reduce the antihypertensive effect of ACE inhibitors. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, which may result in a deterioration of renal function. This effect is usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function (e.g. elderly or dehydrated patients).

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic drugs (insulin or oral antidiabetics) may cause hypoglycaemia. This phenomenon is 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.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Acetylsalicylic acid, thrombolytics and β-blockers
Enalapril can be safely administered concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics and β-blockers.

4.6 Pregnancy and lactation

Use during pregnancy
Enalapril should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed, enalapril should be discontinued as soon as possible and an alternative antihypertensive drug prescribed. Adequately controlled studies have not been performed in humans. A limited number of cases with first trimester exposure have not appeared to manifest malformations consistent with human foetotoxicity.
Enalapril is contraindicated during the second and third trimesters of pregnancy (see section 4.3). Prolonged enalapril exposure during the second and third trimesters may induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).
In case of exposure to enalapril during the second and third trimesters, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken enalapril should be closely observed for hypotension, oliguria and hyperkalaemia. Enalapril, which crosses the placenta, can be removed from the neonatal circulation by peritoneal dialysis, and theoretically may be removed by exchange transfusion.

Use during lactation
Enalapril and enalaprilat are excreted in breast milk, but their effect on the nursing infant has not been determined. Mothers are not recommended to breast-feed during treatment with ACE inhibitors.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Enalaprilat is a metabolite of enalapril. Therefore, during treatment with Enap solution for injection, similar undesirable effects may occur as during treatment with Enap tablets or other ACE inhibitors. In controlled clinical studies with enalaprilat, the most common undesirable effect in hypertensive patients was hypotension (1.8%). Undesirable effects that occurred in more than 1% of patients were also headache (2.9%) and nausea (1.1%). More rare side effects, which occurred in 0.5% to 1% of patients, were myocardial infarction, fatigue, dizziness, fever, rashes and constipation.
Undesirable effects that may occur during treatment with enalapril are classified into the following groups in order of frequency:
- very common (≥1/10),
- common (≥1/100 to <1/10),
- uncommon (≥1/1000 to <1/100),
- rare (≥1/10,000 to <1/1000),
- very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency of undesirable effects listed by individual organ systems:
Blood and lymphatic system disorders
- uncommon: anaemia (including aplastic and haemolytic);
- rare: neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases.

Metabolism and nutrition disorders
- uncommon: hypoglycaemia (see section 4.4).

Nervous system disorders
- common: headache;
- uncommon: paraesthesia, vertigo;
- rare: dream abnormality, sleep disorders.

Eye disorders
- very common: blurred vision.

Cardiac disorders
- very common: dizziness;
- common: syncope, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see section 4.4), chest pain, rhythm disturbances, angina pectoris, tachycardia;
- uncommon: palpitations;

Respiratory, thoracic and mediastinal disorders
- very common: cough;
- common: dyspnoea;
- uncommon: rhinorrhoea, sore throat, hoarseness, bronchospasm/asthma;
- rare: pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders
- very common: nausea;

- common: diarrhoea, 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.

Psychiatric disorders
- common: depression;
- uncommon: confusion, somnolence, insomnia, nervousness;

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

Skin and subcutaneous tissue disorders
- common: rash, hypersensitivity/angioedema (see section 4.4);
- uncommon: diaphoresis, pruritus, urticaria, alopecia;
- rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma.

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

Pregnancy, puerperium and perinatal conditions
- uncommon: impotence;
- rare: gynecomastia.

Vascular disorders
- common: hypotension (including orthostatic hypotension);
- rare: Raynaud's phenomenon.

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

Investigations
- common: hyperkalaemia, increases in serum creatinine;
- uncommon: increases in blood urea, hyponatraemia;
- rare: elevations of liver enzymes, elevations of serum bilirubin.

A symptom complex has been reported: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leukocytosis. Exanthema, photosensitivity and other skin changes may also occur.

If severe undesirable effects occur, treatment should be discontinued.

4.9 Overdose

The most prominent feature of overdosage is hypotension. If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride solution to expand the plasma volume.
During treatment of an overdose, the patient's blood pressure, respiration, serum potassium concentrations and diuresis should be monitored. Enalaprilat can be removed from the circulation by haemodialysis. The haemodialysis clearance of enalaprilat is 0.63 ml/s (38 ml/min) to 1.03 ml/s (62 ml/min); serum enalaprilat concentrations after a four-hour hemodialysis are lower by 45 to 57%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, plain, ATC code: C09AA02.

Enalaprilat inhibits angiotensin-converting enzyme, which catalyses the conversion of angiotensin I to angiotensin II. The inhibition of angiotensin-converting enzyme results in a reduction of angiotensin II concentrations, an increase in plasma renin activity and a reduction of aldosterone secretion.
The antihypertensive effect and haemodynamic effects of enalaprilat in patients with elevated blood pressure are a result of dilation of resistant vessels and a reduction of total peripheral resistance, which gradually reduces blood pressure. Heart rate and cardiac output usually remain unchanged.
Following an intravenous injection, its effect occurs as early as 5 to 15 minutes, the maximum effect in 1 to 4 hours and its action persists for about 6 hours.

5.2 Pharmacokinetic properties

Absorption
Enalaprilat is poorly absorbed after oral administration and is practically inactive; therefore it is administered exclusively intravenously.

Distribution
Following an intravenous injection, it is rapidly distributed to most body tissues, with the highest concentrations in the lungs, kidneys and blood vessels, but there is no evidence that therapeutic doses penetrate the brain. The distribution half-life is 4 hours. 50 to 60% of enalaprilat is bound to serum proteins.

Metabolism
Enalaprilat is not metabolised; 100% of enalaprilat is excreted in the urine.

Elimination
Excretion of enalaprilat is primarily renal. It is a combination of glomerular filtration and tubular secretion. The elimination half-life is about 35 hours.

Renal impairment
In patients with renal insufficiency, the exposure to enalapril and enalaprilat is increased. Elimination is slowed down; therefore, dosage adjustments should be made according to renal function.
Enalaprilat may be removed from the systemic circulation by haemodialysis. The haemodialysis clearance of enalaprilat is 1.03 ml/s (62 ml/min).

5.3 Preclinical safety data

The LD50 for rodents was between 300 and 600 mg/kg following intraperitoneal administration of enalaprilat, >1 g/kg after subcutaneous administration and about 900 mg/kg following intravenous administration. Enalaprilat was not toxic in mice following intraperitoneal and intravenous administration; the LD50 was >7 g/kg and >2 g/kg, respectively. The LD50 of enalaprilat for rats following intraperitoneal and intravenous administration has not been finally determined, but it was >600 mg/kg.

Toxicology studies demonstrated low toxicity of enalapril maleate even after repeated administration; however, high doses administered for a prolonged period of time may cause changes in kidney function and structure. Even repeated intravenous and intramuscular administration of the injection preparation Enap (Krka) had no systemic toxic effects; only tissue damage at the site of administration (blood vessel, muscle) was somewhat more marked in animals receiving enalaprilat than in control animals.

Reproduction toxicity studies showed that enalapril has no teratogenic effects; foetotoxic effects were established in several animal species.
In *in vivo* and *in vitro* tests, enalapril maleate and enalaprilat had no mutagenic effects.
There are no data on possible carcinogenic effects of the drug.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

benzyl alcohol
sodium chloride
sodium hydroxide (E524)
water for injections

6.2 Incompatibilities

Enalaprilat in injection or infusion must not be mixed with amphotericin B and phenytoin because the mixture may become cloudy or a precipitate may form.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Ampoule (colourless tubular glass, Ph. Eur. Type 1 with hydrolytic resistance): 5 ampoules of 1 ml of solution for injection, in a box.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, tovarna zdravil, d. d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

5363-I-792/07

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 October 1991
Date of last renewal: 21 November 2007

10. DATE OF REVISION OF THE TEXT

12 October 2007