Composition
Active substances in 1 tablet: Enalapril maleate 20 mg, Hydrochlorothiazide 6 mg
Active substances in 1 tablet: enalapril maleate 20 mg, hydrochlorothiazide 12.5 mg

The other ingredients are Sodium cross-caramelose, Monohydrate lactose, Magnesium stearate, dyes, Pre-gelatinized maize starch, Sodium hydrogen carbonate.

Pharmaceutical Form and Packaging
14 tablets Co-Renapril 20/6 mg in an ALu/Alu blister; 1 and 2 blisters per pack.
14 tablets Co-Renapril 20/12.5 mg in an ALu/Alu blister; 1 and 2 blisters per pack.

MARKETING AUTHORISATION HOLDER
Balkanpharma-Holding AD
2, Knjaginja Maria Louisa Blvd.
1000 Sofia, Bulgaria

ACTION
Co-Renapril is a combined product for treatment of arterial hypertension (high blood pressure).
The product reduces the enhanced resistance in peripheral vessels, increases heart capacity, without changing heart rate. It positively affects the heart activity at patients with left ventricle hypertrophy.

INDICATIONS
Arterial hypertension, when arterial pressure is not controlled well enough with treatment with ACE-inhibitor only, and/or when stabilization of arterial pressure is obtained with the same doses of the separate components.
NECESSARY INFORMATION BEFORE USE OF THE MEDICINAL PRODUCT

Contraindications
The product is not administered at:
- allergy towards the active substances or some of the ingredients;
- allergic reaction of vascular origin (angioedema) that have occurred at a previous treatment with ACE-inhibitors, or in patients with a congenital or idiopathic angioedema;
- Anuria (stoppage of urine excretion);
- pregnancy and breast-feeding.

SPECIAL PRECAUTIONS FOR USE
Low blood pressure (hypotension) and disorders in the water-electrolyte balance
As with each treatment of high blood pressure, a sharp blood-pressure fall could occur in some patients. This is observed more often at disturbances of the water-electrolyte balance, which might be evoked by treatment with diuretics. Due to this, diuretic treatment should be stopped 2-3 days before starting Co-Renapril therapy and serum electrolytes should be regularly controlled.
A special attention should be paid to patients with brain-vascular disease and with ischemic heart illness, since a sharp decrease in arterial pressure could induce ischemic brain accidents or myocardial infarction.
In case of a blood-pressure decrease, the patient is put in a horizontal position and saline is intravenously administered, if necessary. A transient blood-pressure decrease is not a contraindication for continuation of the therapy.
Aortic stenosis/hypertrophic cardiomyopathy
As all vasodilators, ACE-inhibitors should also be cautiously administered to patients with some heart diseases (hypertrophic cardiomyopathy and sub-aortic stenosis).
Kidney damages
**Co-Renapril** should not be administered to patients with renal insufficiency (creatinine clearance < 80 ml/min and > 30 ml/min). Thiazide diuretics are inappropriate for administration to patients with injured renal function and are not effective in patients with moderate-to-severe renal insufficiency (creatinine clearance of 30 ml/min or less).

In some patients with latent kidney illness, with a bilateral renal artery stenosis or artery stenosis at one kidney only, administration of enalapril together with diuretic could transiently elevate urea and serum creatinine levels; they are normalized after therapy discontinuation.

*Potassium blood levels*

The combination of enalapril with low dose of a diuretic could not exclude the possibility of development of hyperkaliemia (elevated potassium level in the blood).

*Patients with accompanying heart insufficiency*

**Co-renapril** should not be administered as initial therapy in patients with heart insufficiency and hypertension, since a lower enalapril dose is recommended in these cases.

*Liver diseases*

Thiazide diuretics are cautiously administered in patients with injured liver function or progressing liver illness, since even slight disturbances in the water-electrolyte balance could lead to liver coma.

*Effects on metabolism and endocrine glands*

Treatment with thiazide diuretics could elevate the levels of the blood sugar, cholesterol and triglycerides, and could lower the serum levels of sodium, magnesium and potassium.

In some patients, the therapy with thiazide diuretics is associated with an increase in ureic acid and/or gout development. Thiazide diuretics could decrease calcium elimination with urine, as well as to evoke a slight elevation of blood calcium.

*Allergic events - hypersensitivity (angioneurotic edema)*
Angioneurotic edema of face, limbs, lips, tongue, glottis and/or larynx is rarely reported in patients, treated with ACE-inhibitors (incl. enalapril). The edema might occur at any time during the therapy. In such cases, Co-Renapril should be immediately stopped and an appropriate treatment should be carried out. If necessary, 1 mg/ml (0.3-0.5 ml) adrenaline should be immediately administered subcutaneously, and measures to ensure a patent airways should be provided.

During treatment with ACE-inhibitors, an increased rate of angioedema is reported at Negroid patients.

Patients, having in the past angioneurotic edema evoked by other drugs, are with an increased risk of development of such edema at treatment with ACE-inhibitors.

Hypersensitivity reactions, evoked by the product, might be observed in patients with or without manifested allergy or asthma in the past. During therapy with thiazide diuretics, exacerbation of some connective tissue diseases (lupus erythematosus) is also reported.

Cough
At treatment with ACE-inhibitors, occurrence of cough is reported. It is unproductive, long-lasting and fades away after therapy discontinuation.

Surgical interventions/anesthesia
Enalapril lessens organism ability to compensate the blood-pressure decrease in patients subject to surgical interventions and anesthesia with drugs, leading to hypotension. The blood-pressure fall, occurring by this mechanism, could be corrected by infusions.

**DRUG INTERACTIONS AND OTHER FORMS OF INTERACTION**

*Other antihypertensive (blood-pressure decreasing) products*
When Co-Renapril is combined with other antihypertensive products, a mutual enhancement of their effects might occur.

*Serum potassium*
Serum potassium values usually remain within normal range. The use of potassium-supplementing or potassium-sparing products, or electrolyte substitutes, especially in patients with renal damages, could lead to serum-potassium elevation.

Lithium
Diuretics and ACE-inhibitors decrease renal excretion of lithium and increase the risk of lithium intoxication; their simultaneous administration is not recommended.

Non-steroid anti-inflammatory products
The use of NSAIDs could reduce the antihypertensive effect of ACE-inhibitors. In patients with renal injury, treatment with these products could lead to a further decrease of the kidney function; usually, this is reversible.

Non-depolarizing muscle relaxants
Thiazide diuretics could enhance the action of tubocurarine.

Inhibitors of prostaglandin synthesis
Inhibitors of prostaglandin synthesis could reduce the diuretic, natriuretic and antihypertensive effect of diuretics.

SPECIAL WARNINGS IN SPECIFIC GROUPS OF PATIENTS

Administration to children
The safety and efficacy in children has not been studied.

Administration to elderly patients
Clinical investigations on the simultaneous administration of enalapril and hydrochlorothiazide have proved a similar effect and tolerability in elderly and younger patients.

PREGNANCY AND BREAST-FEEDING

Pregnancy
Co-Renapril is not used during pregnancy, unless the therapy is life-saving for the mother.
Administered to pregnant women in the last 6 month of the pregnancy, ACE-inhibitors could lead to a damage and death of the fetus and neonate. In the neonates, hypotension, renal insufficiency, hyperkaliemia and/or skull hypoplasia (skull underdevelopment) could be observed. Oligohydramnion (anomaly of the amnion) has been detected, as manifestation of injured renal function of the fetus. This could lead to limb contractures, deformations of brain-case and facial skull, and to lung underdevelopment.

There is no enough information, concerning the product safety during the first trimester of pregnancy. Presently, there are no data that its use in this period might lead to the above listed undesirable reactions in the embryo and the fetus.

Regular administration of diuretics to healthy pregnant women is not recommended. This exposes mother and fetus to a risk of jaundice at the neonatal, thrombocytopenia (a decreased number of platelets), as well as other possible adverse reactions observed in adults.

In case that Co-Renapril is administered during pregnancy, the patient should be informed about the possible risk for the fetus. In the rare cases of indispensable treatment, regular ultrasound examinations should be conducted in order to estimate the state of the amnion. If changes are found, the therapy should be discontinued, unless it is life-saving for the mother.

Children and mothers, who have taken Co-Renapril should be monitored for low blood pressure, reduced urine amount and elevated blood level of potassium. Enalapril that crosses placenta could be removed from fetus circulation by peritoneal dialysis and (theoretically) by exchange-hemotransfusion. There is no experience, concerning the removal of hydrochlorothiazide (also crossing the placenta) from fetus circulation.

Breast-feeding

Enalapril and hydrochlorothiazide penetrate into mother milk. If their use is imperative, the patient should stop breast-feeding.
EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES
At the beginning of Co-Renapril therapy, a temporary perplexity and vertigo could be observed, which might affect driving and using machines.

DATA ABOUT THE OTHER INGREDIENTS
This medicinal product contains 156 mg of lactose in one tablet, as ingredient. This makes it inappropriate for patients with lactase insufficiency.

INFORMATION FOR PROPER USE
Posology
Medicinal product subject to medical prescription! For oral intake!

Arterial hypertension
Recommended dose - 1 tablet daily Co-Renapril 20/6 mg or Co-Renapril 20/12.5 mg.

After therapy with diuretics
After the initial Co-Renapril dose, a strong blood-pressure decrease could occur, more often at patients on transient therapy with diuretics. Because of this, the treatment with diuretics has to be stopped 2-3 days before the initial administration of Co-Renapril.

Dosing in patients with damaged renal functions
In patients with altered renal fuction

Initial Co-Renapril treatment of patients with altered renal function is not recommended, since in such cases the initial dose is 2.5-5 mg.

OVERDOSE
The most often observed overdose symptoms are associated with development of strong decrease of arterial pressure, disturbances in water-electrolyte balance, dehydration
and renal insufficiency. At overdose anamnesis, the drug use should be stopped and monitoring of the patient by doctor should be provided. The therapy is symptomatic and maintenance. When the drug is taken not long ago, provoking of vomiting, intake of activated charcoal and laxatives are recommended. Water-electrolyte balance and hypotension are corrected by saline venous infusions. Enalapril maleate could be removed from blood circulation by hemodialysis.

POSSIBLE SIDE EFFECTS
Enalapril/hydrochlorothiazide is well tolerated. In clinical trials, the adverse reactions are usually mild and transition, and in the most of cases do not force treatment discontinuation.

The most often side effects, detected in clinical trials, are headache and cough.

Other side effects, reported for enalapril only are:

- general - perplexity, fatigue, weakness;
- cardio-vascular - hypotension, blood-pressure decrease at straightening, heart infarction or brain-vascular accidents (secondary to hypotension at high-risk patients), chest-pain, palpitations, heart-rhythm changes, angina pectoris, Raynaud phenomenon;
- gastrointestinal - ileus, pancreatitis, hepatitis, jaundice, abdominal pain, vomiting, dyspepsia, constipation, lack of appetite, inflammation of mouth mucosa, nausea, diarrhea;
- from the nervous system - depression, perplexity, drowsiness, languor, nervousness, formication, vertigo, sleep disorders, dizziness;
- respiratory - bronchospasm/asthma, choke, nasal secretion, painful throat and rough voice;
- dermal - erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, itching, urticaria, alopecia, rash;
• from the sensory organs - taste disturbances, tinnitus, blurred vision;
• urinary-genital - renal dysfunction, renal insufficiency, reduced urine amount;
• other - hot waves, tongue inflammation, muscle cramps.
A complex could be observed, comprising some of the following symptoms -
temperature raise, inflammation of the serous coats, vascular alterations, muscle
pains, joint pains/arthritus, positive ANA, faster ESR, eosinophilia and leukocytosis.
Rashes, photosensitivity and other dermal phenomena could be observed, too.
• allergic reactions (hypersensitivity/angioedema) - angioneurotic edema on the face,
limbs, lips, tongue, glottis and/or larynx are rare;
• changes in the laboratory indices - usually, no clinically relevant. At enapril
therapy, increase in serum creatinine and urea, liver enzymes and/or serum bilirubin
could be detected. The increase is transient and the values return to normal after
treatment discontinuation. Increased potassium and sodium levels, as well as
reduction of hemoglobin and hematocrit are also observed.

STORING CO-RENAPRIL
At temperature not above 25 °C.

EXPIRY TERM
Two (2) years.
Do not use after the expiry term stated on the packing.

DATE OF LAST REVISION
This leaflet was last approved in March, 2003.