SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE PHARMACEUTICAL PRODUCT

NORMOLOSE tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NORMOLOSE 50 mg Captopril / Tablet
NORMOLOSE 100 mg Captopril / Tablet
For excipients, (see Section 6.1 List of excipients)

3. PHARMACEUTICAL FORM

Tablet
NORMOLOSE 50 mg Captopril / Tablet: White, flat tablets 8 mm in diameter
NORMOLOSE 100 mg Captopril / Tablet, White, flat tablets 10 mm in diameter

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Hypertension : NORMOLOSE is indicated for the treatment of hypertension.
Cardiac Failure : NORMOLOSE, is indicated for the treatment of chronic heart failure, with reduced ventricular systolic function, in combination with diuretics, and in combination with digitalis and beta-blockers, when it is indicated.
Myocardial infarction:

- Short term (4 weeks duration): NORMOLOSE is indicated for the treatment of patients whose clinical condition has been stable within the first 24 hours after myocardial infarction.
- Long term prophylaxis of symptomatic heart failure : NORMOLOSE is indicated for patients with asymptomatic left ventricular dysfunction (ejection fraction ≤ 40%) when in stable clinical condition.

  Type I diabetic nephropathy : NORMOLOSE is indicated for the treatment of Type I diabetic patients with macroglobulinaemic diabetic nephropathy (see Section 5.1 Pharmacodynamics)

4.2. Posology and Mode of Administration

The dose should be individualized according to patient clinical picture (see Section 4.4 Special warnings and special precautions on use) and blood pressure response. The recommended maximum daily dose is 150 mg. NORMOLOSE may be administered before, during or after meals.
Hypertension : The recommended initiation dose is 25-50 mg daily, administered in two divided doses. The dose may be increased gradually, with at least two-week intervals, up to 100-150 mg daily, administered in two divided doses, depending on the target blood pressure level. Captopril may be used alone or in combination with other antihypertensive agents, especially with thiazide diuretics. A once daily dosage may be suitable when a concomitant antihypertensive drug, such as thiazide diuretics is added.
In patients with a potent active renin – angiotensin - aldosterone system (reduced blood volume, renovascular hypertension, and inadequate cardiac feedback), initiation of treatment at a single dose of 6.25 mg or 12.5 mg is preferable.
Initiation of this treatment should preferably take place under strict medical supervision. Following that, these doses should be administered twice daily. The dosage may be increased

gradually up to 50 mg daily, administered in one or two doses and, if necessary, up to 100 mg daily administered in one or two doses.

Heart failure : Treatment of heart failure with captopril should be initiated under close medical supervision. The common initiation dosage is 6.25 mg – 12.5 mg two or three times daily. Titration up to the maintenance dose of 75-150 mg daily should be based on patient clinical condition and tolerance, with an upper limit of 150 mg daily in divided doses. The dose should be increased gradually with two weeks intervals for the evaluation of patient response.

Myocardial infarction :

Short –term treatment : Treatment with captopril should be initiated during hospitalization as soon as possible after the appearance of signs or/and symptoms in patients with stable haemodynamic parameters. A testing dose of 6.25 mg should be administered initially, followed by a dose of 12.5 mg two hours later and 25 mg 12 hours later. From the day after, captopril should be administered in a dose of 100 mg twice daily, for 4 weeks, provided that this can be justified by absence of adverse haemodynamic reactions. Before making any decision regarding the treatment to be implemented after the myocardial infarction stage, patient's condition should be reevaluated at the end of the 4-week treatment.

- *Long-term treatment :* If treatment with captopril is not initiated within 24 hours of the first stage of acute myocardial infarction, initiation is recommended between the 3rd and the 16th day following the infarction, when all the necessary therapeutic conditions (stable haemodynamic parameters and treatment of possible residual ischaemia) have been achieved. Treatment should be initiated during hospitalization under strict medical monitoring (especially of blood pressure) up to the dose of 75 mg. The initial dose should be low (see Section 4.4 Special warnings and special precautions on use), especially when the patient has a normal or low blood pressure at the time of initiation. Treatment should be initiated at a dose of 6.25 mg, followed by a dose of 12.5 mg 3 times daily for two days and by 25 mg 3 times daily, afterwards, if this is justified by the absence of haemodynamic adverse reactions. For an effective cardioprotection, the recommended dosage during long-term treatment is 75 mg up to 150 mg daily, administered in 2 or 3 doses. In cases of symptomatic hypotension, such as in heart failure, the dosage of other concomitant diuretics or/and other vasodilator drugs can be reduced, so that the steady state of captopril can be achieved. If necessary, captopril dose should be readjusted according to the patient clinical reactions. In myocardial infarction captopril can be used in combination with other treatments, such as thrombolytic agents, beta-blockers and acetylsalicylic acid.

Type I diabetic nephropathy : The recommended daily dose of captopril in patients with Type I diabetic nephropathy is 75-100 mg in divided doses. If further reduction in blood pressure is desired, other antihypertensive agents can be co-administered additionally.

Impaired renal function : Since captopril is eliminated mainly by the kidneys, in patients with impaired renal function dosage should be decreased or the dose intervals should be increased.

When a concomitant treatment is administered in patients with severe impairment of renal function, administration of a loop diuretic (e.g. furosemide) is preferred to a thiazide diuretic.

To avoid captopril accumulation in patients with impaired renal function, the following dosages are recommended:

Creatinine clearance (ml/min/1.73 m^2)	Initial daily dose (mg)	Maximum daily dose (mg)
> 40	25-50	150
21-40	25	100
10-20	12.5	75
< 10	6.25	37.5

Elderly patients : As with other antihypertensive drugs, the possibility of starting treatment at a lower initiation dose (6.25 mg twice daily) in elderly patients with possible impaired renal function or dysfunction of other organs must be considered (see above and Section 4.4 Special warnings and special precautions for use).
The dose must be titrated according to blood pressure response to treatment and be maintained in the lowest possible levels required for adequate control of blood pressure.
Children and adolescents : The efficacy and safety of captopril have not been fully evaluated. Administration of captopril in children and adolescents should be initiated under close medical supervision. The initial dose of captopril is approximately 0.3 mg /kg of body weight.
In patients requiring special precautions (children with impaired renal function, premature infants as well as newborns and infants, whose renal function is not as that of older children and adults), the initiation dose should be only 0.15 mg of captopril /kg of body weight. Generally, although in children captopril is administered 3 times daily, the dose and the dose intervals should be individualized according to patient response.

4.3. Contraindications

History of hypersensitivity to captopril, any of the drug's excipients or other ACE inhibitors.
History of angioneurotic oedema associated to previous treatment with an ACE inhibitor.
Inherited/idiopathic angioneurotic oedema.
Second and third trimester of pregnancy (see Section 4.6 Pregnancy and lactation).
Lactation (see Section 4.6 Pregnancy and lactation)

4.4. Special warnings and special precautions for use

Hypotension : Hypotension can rarely occur in non-selective hypertensive patients. Symptomatic hypotension is more likely to occur in hypertensive patients with hypovolaemia or/and sodium reduction due to intensive treatment with diuretics, inhibited sodium consumption in their daily diet, diarrhoea, vomiting or haemodialysis. Hypovolaemia or/and sodium reduction must be corrected before the administration of an ACE inhibitor, whereas initiation of treatment at a lower dose must be considered. Patients with heart failure are at higher risk of hypotension and it is recommended to initiate the treatment with an ACE inhibitor at a lower initial dose. Caution should be exercised when increasing the dose of captopril or diuretics in patients with heart failure. As with other antihypertensive agents, excessive reduction in blood pressure in patients with ischaemic heart disease or cerebrovascular disease can increase the risk of myocardial infarction or stroke. If hypotension develops, the patient must be placed in supine position. Volume repletion with normal saline intravenous administration might be necessary.
Renovascular hypertension : There is an increased risk of hypotension and renal failure during treatment with an ACE inhibitor in patients with bilateral renal artery stenosis, or artery stenosis in a single functioning kidney. Loss of renal function may be accompanied with only slight changes in serum creatinine. In such patients, treatment should be initiated at low doses, under close medical supervision, careful titration and renal function monitoring.
Impaired renal function: In cases of impaired renal function (creatinine clearance ≤40 ml/min), the initial dose of captopril should be re-adjusted according to creatinine clearance (see Section 4.2_Posology and Mode of Administration) and, afterwards, according to patient response. Monitoring of serum potassium values and creatinine on a regular basis is part of the common clinical practice in these patients.
Angioedema : Angioedema of the extremities, face, lips, mucous of the tongue, glottis or larynx may occur in patients under treatment with ACE inhibitors, especially within the first two weeks following treatment initiation. However, severe angioedema can rarely develop after long – term treatment with an ACE inhibitor. In these cases, treatment should be discontinued immediately. Tongue, glottis or larynx angioedema may be fatal. Therefore,

emergency treatment should be initiated immediately. The patient must be hospitalized and monitored for at least 12 to 24 hours and not released until the complete eradication of the symptoms.

Cough: Cough has been reported following the administration of ACE inhibitors. Characteristically, the cough is non-productive, persistent and stops after treatment discontinuation.

Hepatic impairment : ACE inhibitors have rarely been connected to a syndrome commencing with cholestatic jaundice and progressing to acute hepatic necrosis and (occasionally) death. The pathophysiology of this syndrome has not been elucidated. Patients taking ACE inhibitors and developing jaundice or exhibiting notably increased liver enzymes should discontinue treatment with ACE inhibitors and be under appropriate medical care.

Hyperkalaemia : Increases in plasma potassium have been observed in certain patients who are under treatment with ACE inhibitors, including captopril. Patients with renal failure, diabetes mellitus or those under concomitant treatment with potassium- sparing diuretics, potassium supplements or sodium substitutes containing potassium or patients receiving other medications related to serum potassium increases (e.g. heparin), are among those with increased risk of developing hyperkalaemia. If concomitant administration of the aforementioned agents is considered appropriate, frequent monitoring of serum potassium is recommended.

Lithium : The combination of lithium and captopril is not recommended (see Section 4.5 Interactions with other medicinal products and other forms of interaction)

Aortic and mitral valve stenosis / Hypertophic obstructive cardiomyopathy/: ACE inhibitors should be administered with caution to patients with severe stenosis of the valves and the ejection area of the left ventricle, and should be avoided in case of cardiogenic shock with haemodynamically severe obstruction.

Neutropenia/ agranulocytosis : Neutropenia / agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, including captopril. Patients with normal renal function or without any other potentially complicating factors, rarely develop neutropenia. Captopril should be administered with extreme caution to patients with vascular collagen disease, patients receiving immunosuppressive drugs, allopurinol or procainamide, or a combination of these agents, especially with pre-existing impaired renal function. Some of these patients developed severe infections, not responsive to the administration of intensive antibiotic therapy.

In case captopril is administered to these patients, it is indicated to count the number and the type of white blood cells prior to initiation of the treatment, every two weeks during the first three months of therapy with captopril and, after that, periodically. During treatment, patients should be instructed to report any sign of infection they observe (e.g. soar throat, fever) and after that a white blood cell type determination should be performed. Captopril and other concomitant medications (see Section 4.5 Interactions with other medicinal products and other forms of interaction) should be discontinued in case of detected or suspected neutropenia (neutrophils count lower than $1000/mm^3$). In most patients, the number of neutrophils returns to normal levels soon after captopril treatment discontinuation.

Proteinuria : Can occur especially to patients with existing impaired renal function or upon the administration of relatively high doses of ACE inhibitors.

Whole urinary protein excretion, higher than 1g daily, has been observed in approximately 0.7% of patients receiving captopril. Most of these patients had indications of previous renal disease or had received relatively high doses of captopril (higher than 150 mg /daily) or both. Nephrotic syndrome occurred in one fifth of proteinuric patients. In most cases, proteinuria regressed or disappeared within six months, regardless of continuing captopril treatment or not. Rarely, changes in parameters of renal function, such as BUN and creatinine, have occurred in patients with proteinuria.

Patients with previous renal disease should undergo a measurement of protein urinary excretion (first – void sample) before initiation of treatment and, afterwards, periodically.

Anaphylactic reactions during desensitization : There have been rare reports of prolonged, life – threatening anaphylactic reactions in patients receiving ACE inhibitors and undergo desensitization treatment with Hymenoptera virus. In such patients the reactions were avoided by the temporary discontinuation of the ACE inhibitor treatment, but reappeared during involuntary re-provocation. Thus, caution should be exercised with patients under treatment with ACE inhibitors who undergo desensitization procedures.

Anaphylactic reactions during high flow dialysis/exposure to membrane lipoprotein removal: There have been reports of anaphylactic reactions in patients undergoing dialysis with high flow dialysis membranes or low density lipoprotein removal with dextran sulphate absorption. In such patients, a different type of dialysis membrane should be used or a different medication category should be administered.

Surgery/anaesthesia : Hypotension may occur to patients undergoing a major surgical operation or during the administration of anaesthetic agents known to reduce blood pressure. In such cases, hypotension may be treated with volume dilatation.

Diabetic patients : Blood glucose levels should be closely monitored in diabetic patients previously treated with an oral antiglycaemic agent or insulin, mainly during the first month of treatment with an ACE inhibitor.

Lactose : Since NORMOLOSE contains lactose, it should not be administered in cases of inherited galactosaemia, malabsorption of glucose and lactose or in the presence of lactose deficiency syndrome (rare metabolic diseases).

Ethnic differences : As with other angiotensin converting enzyme inhibitors, captopril is obviously less effective in reducing blood pressure in the coloured population compared to the non-coloured population, possibly due to the higher prevalence of low renin cases among the coloured hypertensive patients.

4.5. Interactions with other medicinal products and other forms of interaction

Lithium : Reversible increases of serum lithium and lithium toxicity have been reported during concomitant administration of lithium and ACE inhibitors.

Concurrent use of thiazide diuretics may increase the risk for lithium toxicity and enhance the already increased risk for lithium toxicity with ACE inhibitors. Administration of captopril together with lithium is not indicated and careful monitoring of serum lithium levels should be performed if this combination is considered necessary (see Section 4.4 Special warnings and special precautions for use).

Potassium sparing diuretics or potassium supplements : ACE inhibitors reduce urinary potassium secretion. Potassium sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements or sodium substitutes which contain potassium, may lead to increased values of serum potassium. If concomitant administration is indicated due to hypokalaemia, caution should be exercised during administration and frequent monitoring of serum potassium levels should be performed (see Section 4.4 Special warnings and special precautions for use).

Diuretics (thiazide diuretics or loop diuretics) : Previous treatment with high doses of diuretics may lead to hypovolaemia and an increased risk for hypotension upon initiation of treatment with captopril (see Section 4.4 Special warnings and special precautions for use). Hypotensive symptoms may be reduced with discontinuation of the diuretic, increase of the volume or sodium intake or with low initiation doses of captopril. However, no clinically significant interactions with hydrochlorothiazide or furosemide have been observed in specific studies.

Other antihypertensive agents : Captopril has been administered with safety in combination with other commonly prescribed antihypertensive agents (e.g. beta-blockers and long acting

calcium-channel blockers). Concomitant administration of these agents may increase the hypotensive effect of captopril.

Glyceryl trinitrate and other nitrates or other vasodilators, should be administered with caution.

Management of acute myocardial infarction : Captopril can be concomitantly administered with acetylsalicylic acid (in cardiac doses) , thrombolytics, beta-blockers and /or nitrates in patients with myocardial infarction.

Tricyclic antidepressants / Antipsychotics : ACE inhibitors may enhance hypotensive effects of certain tricyclic antidepressants and antipsychotic products (see Section 4.4 Special warnings and special precautions for use). Orthostatic hypotension may occur.

Allopurinol procainamide, cytostatics or immunosuppressant agents : Concomitant administration with ACE inhibitors may lead to an increased risk of leucopenia, especially if they are used in higher doses than recommended.

Non-steroidal anti-inflammatory drugs : It has been reported that non-steroidal anti-inflammatory drugs (NSAIDs) and ACE inhibitors have an additive effect in increasing serum potassium, whereas they can impair renal function. These effects are generally reversible. Rarely, acute renal failure may occur in patients with impaired renal function, such as the elderly and the dehydrated patients. Long term use of NSAIDs may decrease the antihypertensive effect of ACE inhibitors.

Sympathomimetics : They may reduce the antihypertensive effects of ACE inhibitors. Patients should be carefully monitored.

Antidiabetic agents : Pharmacological studies have shown that, regarding the blood glucose reduction, ACE inhibitors , including captopril may enhance the actions of insulin as well as other oral antidiabetic agents, such as sulphonylurea. If this occurs, a decrease in dosage of antidiabetic agents during concomitant administration with ACE inhibitors, may be necessary.

Clinical chemistry.

The presence of captopril may lead to a false positive result in acetone urinary test.

4.6. Pregnancy and lactation

Use during Pregnancy: NORMOLOSE administration is not indicated during the first trimester of pregnancy. An alternative therapy should be administered as soon as possible, when a pregnancy is planned or confirmed.

No controlled studies have been conducted with humans, however a limited number of exposed pregnancies during the first trimester of pregnancy have not shown any congenital anomalies.

NORMOLOSE administration is contra-indicated during the second and the third trimester of pregnancy. Prolonged exposure to captopril during the second and the third trimester is known to cause toxicity in the foetus (impaired renal function, inadequate amniotic fluid, retardation of cranial calcification) and in newborns (neonatal renal failure, hypotension, hyperkalaemia) (see also Section 5.3 Preclinical safety data)

Use during Lactation: NORMOLOSE administration is contra-indicated during lactation.

4.7. Effects on the ability to drive and use machines

As with other antihypertensive drugs, captopril may reduce the ability to drive and handle machinery, especially upon initiation of treatment and dose adjustments or if it is used together with alcohol. However, this depends upon the sensitivity of each individual.

4.8. Undesirable effects

The undesirable events that have been reported with the use of captopril or/and ACE inhibitors include :

Blood and the lymphatic system disorders:

Very rare : Neutropenia/agranulocytosis (see Section 4.4 Special warnings and special precautions for use), pancytopenia especially in patients with impaired renal function (see Section 4.4 Special warnings and special precautions for use), anaemia (including aplastic and haemolytic anaemia), thrombocytopenia, lymphadenopathy, eosinophilia, autoimmune disorders and/or positive ANA titres.

Metabolism and nutrition disorders :

Rare : Anorexia

Very rare : Hyperkalaemia, hypoglycaemia (see Section 4.4 Special warnings and special precautions for use)

Psychiatric disorders :

Common: Sleep disturbances

Very rare : Confusion, depression

Nervous system disorders :

Common: Taste disturbances, dizziness

Rare : Nystagmus, headache and paraesthesias

Very rare : Stroke, including cerebral apoplexy and syncoptic episode

Eye disorders :

Very rare : Blurred vision

Cardiac disorders :

Uncommon: Tachycardia, tachyarrhythmia, angina, palpitation

Very rare : Heart attack, cardiogenic shock

Vascular disorders :

Uncommon: Hypotension (see Section 4.4 Special warnings and special precautions for use), Raynaud's syndrome, erythema, pallor

Respiratory, thoracic and mediastinal disorders :

Common: Dry, irritating, non-productive cough, (see Section 4.4 Special warnings and special precautions for use) and dyspnoea

Very rare: Bronchospasm, rhinitis, allergic alveolitis/ eosinophilic pneumonia

Gastrointestinal disorders:

Common: Nausea, vomiting, gastric irritation, abdominal pain, diarrhoea, constipation, dry mouth

Rare: Stomatitis, aphthoid ulcerations

Very rare: Glossitis, peptic ulcer, pancreatitis

Hepato-biliary disorders :

Very rare : Impaired liver function and cholestasis (including jaundice), hepatitis including necrosis, increased serum liver enzymes and bilirubin

Skin and subcutaneous tissue disorders

Common: Pruritus with or without rash, rashes and alopecia

Uncommon: Angioedema (see Section 4.4 Special warnings and special precautions for use)

Very rare : Urticaria, Stevens Johnsons Syndrome, erythema multiforme, photosensitivity, skin redness, pemphigoid reactions, exfoliative dermatitis

Musculoskeletal disorders, connective tissue and bone disorders

Very rare : Myalgia, arthralgia

Renal and urinary disorder

Rare: Disorders in renal function including renal failure, polyuria, oliguria, increased frequency of urination

Very rare: Nephrotic syndrome

Reproductive system and breast disorders

Very rare: Impotence, gynaecomastia

General disorders :

Uncommon: Chest pain, fatigue, illness

Very rare: Fever

Investigations:
Very rare: Proteinuria eosinophilia, increased serum potassium, decreased serum sodium, increased serum urea, creatinine and serum bilirubin, decreased haemoglobin, hematocrit, white blood cells, thrombocythaemia, positive ANA titre, increased erythrocyte sedimentation rate.

4.9. Overdose

Overdose symptoms include severe hypotension, shock, lethargy, bradycardia, electrolyte disturbance and renal failure.
In case of current drug abuse, certain measures should be taken in order to prevent absorption (e.g. gastric lavage, administration of drugs that reduce absorption and sodium sulphate within 30 minutes after taking) and enhance drug excretion.
If hypotension occurs, patient should be placed in supine position and sodium supplements as well as fluids should be administered immediately. Parasympathetic nervous system side effects should be treated with atropine administration. In this case cardiac pacing may be considered.
Captopril may be eliminated from the circulation with haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

Pharmacotherapeutic category : ACE inhibitors, ATC code : C09AA01.
Captopril is a highly selective antagonistic Angiotensin Converting Enzyme inhibitor I (ACE inhibitors).
The beneficial effects of ACE inhibitors seem to emerge primarily from the suppression of plasma renin – angiotensin – aldosterone system. Renin is an endogenous enzyme which is synthesized by the kidneys and released in the circulation, where it converts angiotensinogen to angiotensin I, a relatively inactivated decapeptide. Subsequently, angiotensin I is converted to angiotensin II by the peptidylpeptidase angiotensin converting enzyme. Angiotensin II is a potent vasoconstrictor responsible for vascular contraction and the increase in blood pressure, as well as the activation of adrenals to secrete aldosterone. ACE inhibition results in the decrease of plasma angiotensin II, which leads to a vasodilatation effect and a decrease in aldosterone secretion. Despite the latter decrease being small, minor increases in serum potassium concentrations as well as loss of sodium and fluids might occur. Discontinuation of angiotensin II negative feedback on renin secretion results in an increase in plasma renin activity.
Another effect of the converting enzyme is the degradation of bradykinin, a potent vasosuppressant kinin peptide, into inactivated metabolites.
Therefore, ACE inhibition results to increased activity of the circulating and local kallikrein-kinin system, which contributes to peripheral vasodilatation by activating the prostaglandin system. This mechanism is possibly involved in the hypotensive effect of ACE inhibitors and is responsible for certain adverse events of this drug category.
Maximum reductions in blood pressure usually occur within 60 to 90 minutes following oral administration of a single dose of captopril. The duration of actions is dose – dependent. The reduction in blood pressure may be gradual.
Thus, several weeks of treatment may be necessary in achieving the maximum therapeutic benefits. Captopril and thiazide diuretics effects in blood pressure reduction are additive.
In patients with hypertension, captopril reduces blood pressure in the supine and standing position, causing neither any feedback increase in heart rate nor water or sodium retention.

Captopril has caused a notable reduction in peripheral vascular resistance in haemodynamic tests. Generally, no clinical relevant changes in plasma renal flow or glomelular filtration rate have occurred.

In most patients, the antihypertensive effect of captopril starts approximately 15 to 30 minutes after the administration of an oral dose. The maximum effect was achieved after 60 to 90 minutes. Generally, the maximum reduction in blood pressure of a predetermined dose of captopril became obvious after 3 or 4 weeks.

The antihypertensive effect of the recommended daily dose is preserved even under long-term treatment. Temporary discontinuation of captopril treatment does not provoke any rapid and excessive increase in blood pressure (rebound effect). Treatment of hypertension with captopril leads to a reduction in left ventricular hypertrophy.

Haemodynamic tests have shown that, in patients with heart failure, captopril reduced peripheral systemic resistance and increased venous capacity with a reduction in cardiac pre- and post load (a decrease in the filling pressure of the ventricle). Additionally, it has been observed that treatment with captopril results to increased blood volume per minute, work index and exercise ability.

In a large, placebo controlled clinical study, it was shown that in patients with left ventricular dysfunction (LVEF ≤40%) after myocardial infarction, captopril (the administration of which started between the 3rd and the 16th day after the infarction) prolonged survival and reduced cardiovascular mortality. The later became obvious by the retardation of symptomatic heart failure and the decrease in the need for hospitalization due to heart failure compared to placebo.

A decrease in subsequent infarctions in revascularization processes and/or in the need for administration of additional treatment with diuretics or/ and digitalis or for an increase in their dose has also occurred when compared to placebo. A retrospective analysis has shown that captopril decreased the reoccurrence of infarction and the revascularization processes (none of the above constituted study end–points).

Another large, placebo controlled clinical study in patients with myocardial infarction, has shown that captopril (administered within 24 hours following the episode and for one month) significantly reduced overall mortality after 5 weeks when compared to placebo. The beneficial effect of captopril in overall mortality continued to be traceable one year later. No indication of negative effect related to premature mortality during the first day was found.

The cardioprotective effects of captopril become obvious regardless of patient age and gender, the localization of the infarction and the established effective concomitant treatment during post–infarction period (thrombolytic agents, beta- blockers and acetylsalicylic acid.

Type I diabetic nephropathy

In a multicentre, double blind, placebo–controlled, clinical study on insulin dependent (Type I) diabetic patients with proteinuria, with or without hypertension (concomitant administration of other antihypetensives for blood pressure control was allowed), captopril significantly reduced (by 51%) the duplication time of the initial creatinine concentration when compared to placebo. The frequency of end – stage renal failure (haemodialysis, tranplantation) or death was significantly lower with captopril when compared to placebo (51%). In patients with diabetes and microproteinuria treatment with captopril reduced protein excretion within two years.

The effects of treatment with captopril on retaining renal function constitute an additional benefit to that which may have arisen from the reduction in blood pressure itself.

5.2. Pharmacokinetics

Captopril is an orally administered active agent and its action does not require biotransformation. The mean minimum absorption is approximately 75%. The peak plasma concentration is achieved within 60-90 minutes. The presence of food in the gastrointestinal

system decrease absorption by 30-40 %. Approximately 25-30% of the circulating drug binds to plasma proteins.

The apparent elimination time of non-metabolized captopril in blood is 2 hours. Over 95% of the absorbed dose is excreted in the urine within 24 hours. 40-50% is non-metabolized drug and the rest are non–active bisulphate metabolites (captopril bisulphate and captopril cysteine bisulphate).

Impaired renal function may cause drug accumulation. Therefore, a dose reduction or/and extension of dose intervals should be implemented in patients with impaired renal function (see Section 4.2 Posology and Mode of Administration). Experimental studies on animals have shown that captopril does not cross the hematoencephalic barrier to a significant extent.

5.3. Preclinical safety data

Although studies with captopril conducted on animals during organogenesis have not shown any teratogenic effect, in some species captopril has caused embryotoxicity, including embryonic mortality during late pregnancy, growth retardation and postnatal mortality in rats. Preclinical data do not reveal any special risk for humans based on conventional studies for pharmacological safety, toxicity with repeated doses, gonadotoxicity and tumorogenic effect.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients:

Lactose Monohydrate
Starch Maize
Magnesium Stearate
Cellulose Microcrystalline

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4. Special precautions for storage

Store at room temperature (< 25° C)

6.5. Nature and contents of the container

PACKAGE: Box X 20 (Aluminum and PVC blister 2 X 10 TABS)

6.6. Instructions for use and handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

ADELCO – CHROMATOURGIA ATHINON E. COLOKOTRONIS BROS S.A.,
37 PIREOS STR.,
MOSCHATO,
ATHENS,
GREECE

8. MARKETING AUTHORISATION NUMBERS

Normolose 50 mg : MA072/00402
Normolose 100 mg : MA072/00403

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

4th October 2005

10. DATE OF REVISION OF THE TEXT

adelco

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