NORMOLOSE 50MG
(Captopril)

PATIENT INFORMATION LEAFLET

1. DEFINITION OF THE MEDICINAL PRODUCT

1.1 Name of the medicinal product
NORMOLOSE 50MG

1.2 Composition
Active ingredient: Captopril
Excipients:
Tablets 50 mg: Lactose Monohydrate, Starch Maize, Magnesium Stearate, Cellulose Microcrystalline.

1.3 Pharmaceutical form
Tablets 50 mg: White, flat tablets on one side scored and with the inscription ‘‘ADELCO’’ on the other.

1.4 Active ingredient content
Each Normolose tablet 50 mg contains 50 mg Captopril.

1.5 Description-packaging
- BT x 20 tablets (2 PVC/ALU blisters x 10 tabs)
- BT x 1000 tablets (100 PVC/ALU blisters x 10 tabs)
(Not all pack sizes may be marketed)

1.6 Pharmacotherapeutic category
ACE Inhibitors

1.7 Marketing Authorization Holder-Manufacturer:
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2. WHAT YOU SHOULD KNOW ABOUT THE DRUG PRESCRIBED BY YOUR PHYSICIAN

2.1 General Information
Captopril is a particularly selective, competitive inhibitor of angiotensin-I - converting enzyme (ACE inhibitors).
In patients with hypertension, captopril causes a reduction in the arterial pressure both in a supine and upright body position, without leading to any compensatory increase of cardiac frequency, nor to any water or sodium retention.
In most patients, the antihypertensive action commences approximately 15 to 30 min after the oral administration of captopril. The maximum activity was accomplished after 60 to 90 minutes. The maximum reduction in the arterial pressure of a pre-determined dose of captopril is observed in general after 3 or 4 weeks. The temporary discontinuation of treatment with captopril does not cause any rapid, excessive increase in the arterial pressure.

In patients with cardiac insufficiency captopril leads to a decrease in the peripheral systemic resistance and to an increase in the venous capacity. This leads to a decrease in the preload and afterload of the heart (a decrease in the filling pressure of the left ventricle). In addition, in the treatment with captopril, an increase in the cardiac output, in the index of heart activity and in the ability to exercise have been observed.
A retrospective analysis showed that captopril reduced the re-occurrence of infarction and the procedures of heart revascularization.

Nephropathy due to diabetes mellitus type I
In a multicentre clinical trial in insulin-dependent (type I) diabetic patients with proteinuria, with or without hypertension, captopril significantly reduced the doubling time of the initial concentration of creatinine, in comparison with the placebo drug. The frequency of terminal stage renal insufficiency (haemodialysis, transplantation) or death was significantly lower with captopril. In patients with diabetes and microproteinuria, the treatment with captopril reduced the excretion of protein within a time period of two years.
The effects of treatment with captopril upon the maintenance of the renal function are furthermore to the benefit that may have resulted from the reduction in the arterial pressure.

2.2 Indications
Hypertension: NORMOLOSE is indicated for the therapeutic treatment of hypertension.

Cardiac insufficiency: NORMOLOSE is indicated for the therapeutic treatment of chronic cardiac insufficiency, with a decrease in the systolic ventricular function, along with diuretics, and in cases that this is indicated, with digitalis and β-blockers.

Myocardial infarction:
- *short-term treatment (duration of 4 weeks)*: NORMOLOSE is indicated in every patient, whose clinical condition is stable within the first 24 hours after an episode of myocardial infarction.
- *long-term prophylaxis of symptomatic cardiac insufficiency*: NORMOLOSE is indicated in patients whose clinical condition is stable with an asymptomatic dysfunction of the left ventricle (ejection fraction ≤ 40%).

Nephropathy due to diabetes mellitus type I : NORMOLOSE is indicated for the therapeutic treatment of macroproteinuric diabetic nephropathy in patients with diabetes mellitus type I.

2.3 Contra-indications
- A history of hypersensitivity to captopril, to any of the drug's excipients or to any other ACE inhibitor.
- A history of angioneurotic oedema that is related to a previous treatment with an ACE inhibitor.
- Hereditary / idiopathic angioneurotic oedema.
- Second and third trimester of pregnancy.

Do not take NORMOLOSE if you are more than 3 months pregnant. (It is also better to avoid NORMOLOSE in early pregnancy – see pregnancy section).

2.4 Special precautions and warnings for use
2.4.1 In general
Before receiving this drug inform your doctor of any health problem that you may possibly have. You should know the following for this drug.

- Hypotension is rarely observed in non-complicated hypertensive patients. In addition, rarely has symptomatic hypotension been reported in hypertensive patients that have undergone a circulatory volume reduction or / and sodium reduction due to intensive treatment with diuretics, due to a prohibition to use salt in their diet, diarrhoea, vomiting or haemodialysis. The reduction in volume or / and sodium must be corrected prior to the administration of an ACE inhibitor, whereas the case of initiation of treatment with a lower dose should be examined.
The patients that suffer from cardiac insufficiency are at a higher risk of hypotension and therefore the commencement of therapeutic treatment with a lower initial dose is recommended. Care should be exercised each time the dose of captopril or of a diuretic is increased in patients with cardiac insufficiency.
In the case of hypotension, the patient should be placed in a supine position. The replacement of circulatory volume might be needed with the intravenous administration of normal saline.
It is recommended that the patients ask for their doctor's advice.

- In patients with renovascular hypertension there is an increased risk of hypotension and renal insufficiency. In these patients, treatment should commence under strict medical surveillance with low doses, careful titration and monitoring of the renal function.
- In patients with renal insufficiency (creatinine clearance ≤ 40 ml/min), the initial dose of captopril should be readjusted in accordancewith the value of the patient's creatinine clearance (see 2.6 Dosage), and subsequently depending on the patient's correspondence to treatment. In these patients the serum levels of potassium and creatinine should be systematically monitored.
- The patients who receive ACE inhibitors, who demonstrate jaundice or display a significant increase in the levels of hepatic enzymes, should discontinue treatment with ACE inhibitors and should receive the respective medical care.
- Increases in serum levels of potassium have been observed in some patients who receive ACE inhibitors, including captopril. Patients who are at risk of developing hyperkalaemia include those who suffer from renal insufficiency, diabetes mellitus, or those who receive an accompanying treatment with diuretics that retain potassium, with potassium supplements or salt substitutes that contain potassium, or those patients who receive other drugs that are related with increases in the serum levels of potassium (for example, heparin). If the simultaneous administration of the above mentioned factors is considered to be appropriate, the regular monitoring of the serum levels of potassium is then recommended.
- ACE inhibitors should be administered with care in patients with aortic and mitral valve stenosis / obstructive hypertrophic cardiomyopathy.
- Cough has been reported with the administration of ACE inhibitors.
- The combination of lithium and captopril is not recommended.
- Angioedema of the patient's extremities, face, lips, mucosa, tongue, glottis or larynx may manifest in patients who receive ACE inhibitors, especially during the first weeks after the commencement of treatment. However, in rare occasions, a severe angioedema may develop after the long-term use of an ACE inhibitor. The patients are recommended to immediately report to their doctor any signs or symptoms that indicate angioedema and to discontinue their therapy.
- Neutropenia / agranulocytosis, thrombocytopenia and anaemia have been reported in patients who receive ACE inhibitors, including captopril. Captopril should be administered with extreme caution in patients with vascular disease of collagen, in patients who receive immunosuppressive treatment, treatment with allopurinol or procainamide, or some combination of these agents, especially on

the grounds of a pre-existing renal dysfunction. Some of these patients developed severe infections.

- Proteinuria may occur, especially in patients with pre-existing renal impairment, or with relatively high doses of ACE inhibitors. Nephrotic syndrome occurred in approximately one fifth of the patients with proteinuria. Patients with a previous renal disease must perform a urine protein quantification (first morning urine sample) prior to initiating therapy and afterwards on a periodic base.
- The patients are recommended to immediately report any evidence of infection (for example, sore throat, fever) which may be a symptom of neutropenia / agranulocytosis, or of a progressively developing oedema that may be associated with proteinuria and nephrotic syndrome.
- In rare occasions anaphylactoid reactions have been reported in patients who receive ACE inhibitors and undergo a desensitization treatment with Hymenoptera venom. The patients should be recommended to seek advice from their doctor.
- Anaphylactoid reactions have been reported in patients who perform haemodialysis with high-flux diffusion membranes or undergoing low-density lipoprotein apheresis with dextran sulphate absorption.. In these patients, a different type of haemodialysis membrane should be used, or they should receive a different type of drug.
- If the patient is to be surgically operated upon, the attending doctor should be informed that he/she is receiving captopril.
- Glucose levels should be closely monitored in diabetic patients who have been previously treated with an orally administered antidiabetic drug or with insulin, mainly during the first month of therapeutic treatment with an ACE inhibitor.
- You must tell your doctor if you think you are (or might become) pregnant. NORMOLOSE is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

2.4.2 Pregnancy and breast-feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking NORMOLOSE before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of NORMOLOSE.

NORMOLOSE is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. Breast-feeding newborn babies (first few weeks after birth), and especially premature babies, is not recommended whilst taking NORMOLOSE.

In the case of an older baby your doctor should advise you on the benefits and risks of taking NORMOLOSE whilst breast-feeding, compared with other treatments.

2.4.3 Effect on the ability to drive and use machines

As it may occur with the other antihypertensive drugs as well, the ability to drive and use machines may be reduced, mainly during the commencement of the treatment or upon

the modification of the dosage, and also in combination with the use of alcohol, this however depends upon the sensitivity of each individual.

2.4.4 Special warnings about the contained excipients.
Lactose: NORMOLOSE contains lactose, and should therefore not be administered in cases of congenital galactosaemia, glucose and galactose malabsorption, or at the presence of lactase insufficiency syndromes (rare metabolic diseases).

2.5 Interactions with other drugs or other forms of interaction
You should inform your doctor for all the medications you are receiving. In these medications the drugs that you received without a doctor's prescription are also included.
The active substances of NORMOLOSE may interact with other drugs, such as:

- Potassium sparing diuretics or potassium supplements.
- Diuretics.
- Other antihypertensiveagents.
- Therapeutic treatment for acute myocardial infarction.
- Lithium (see also 2.4 Precautions and warnings on use).
- Tricyclic antidepressants / antipsychotic drugs.
- Allopurinol, procainamide, cytostatic or immunosuppressive factors.
- Non-steroidal anti-inflammatory drugs.
- Sympathomimetic drugs.
- Antidiabetic drugs.

Captopril may lead to a false positive urine test for acetone.

2.6 Dosage
NORMOLOSE is for oral use.
You should receive NORMOLOSE strictly in accordance with your doctor's instructions. If you have any doubts, please ask your doctor or your pharmacist.
The dose should be individualized according to the clinical presentation of the patient and to the response of his/her arterial pressure. The recommended maximum daily dose is 150 mg. NORMOLOSE can be administered prior to, during and after meals.
Hypertension: the recommended initial dose is 25-50 mg daily, administered in two divided doses. The dose may be gradually increased, with time intervals of at least 2 weeks, to 100-150 mg daily administered in two divided doses, depending on the needs to acquire the desirable arterial pressure. Captopril may be used alone or with other antihypertensive agents, particularly thiazide diuretics. A once-daily dosing regimen may be appropriate when an accompanying antihypertensive drug is added, such as thiazide diuretics.
In patients with extremely active renin-angiotensin-aldosterone system (decreased blood volume, renovascular hypertension, insufficient cardiac compensation) it is more preferable to commence treatment with a simple dose of 6.25 mg or 12.5 mg. The commencement of this therapy should preferably take place under strict medical supervision. These doses will then be administered at a rate of two per day. The dosage may be gradually increased 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.

Cardiac insufficiency: treatment with captopril for cardiac insufficiency should commence under strict medical surveillance. The usual dose to commence therapy is 6.25 mg – 12.5 mg two or three times daily. The titration to the maintenance dose
(75-150 mg daily) should be conducted according to the patient's response, his/her clinical condition and tolerance, with a maximum limit of 150 mg daily in divided doses.

The dose should be gradually increased, in time intervals of at least 2 weeks in order to evaluate the patient's response.

Myocardial infarction:
- *short-term treatment:* the treatment with captopril should commence in hospital as soon as possible after the demonstration of signs or / and symptoms in patients with stable haemodynamic parameters. An initial testing dose of 6.25 mg should be administered, followed by a dose of 12.5 mg 2 hours later and by a dose of 25 mg 12 hours later. The next day, captopril should be administered in a dose of 100 mg daily, in two daily administrations, for 4 weeks, if this is justified by the absence of undesirable haemodynamic reactions.
At the end of the 4 week treatment, the patient's condition needs to be re-evaluated, prior to making the decision concerning the treatment that is to be followed at the stage following the myocardial infarction.
– *chronic treatment:* If treatment with captopril does not commence within the first 24 hours of the first stage of an acute myocardial infarction, it is recommended to commence between the 3rd and 16th day after the infarction, when the necessary therapeutic conditions have been accomplished (stable haemodynamic parameters and management of the possible residual ischaemia). Therapeutic treatment should commence at hospital under strict monitoring (mainly of the arterial pressure) up to the dose of 75 mg. The initial dose should be low, particularly in the case that the patient has a normal or low arterial pressure during the commencement of treatment. Treatment should start with a dose of 6.25 mg, followed by a dose of 12.5 mg 3 times daily for 2 days and then 25 mg 3 times daily, if this is justified by the absence of undesirable haemodynamic reactions.
The recommended dose for an efficient heart protection during long-term treatment is 75 to 150 mg daily, administered in 2 or 3 doses. In cases of symptomatic hypotension, as in cardiac insufficiency, the dose regimen of the diuretics or / and the other accompanying vasodilating drugs may be decreased, so as to accomplish a dose of steady state of captopril. In the cases that this is necessary, the dose of captopril must be readjusted according to the clinical reactions of the patient. Captopril may be used in combination with other therapeutic treatments in myocardial infarction, such as thrombolytic factors, β-blockers and acetylsalicylic acid.

Nephropathy due to diabetes mellitus type I: in patients with nephropathy due to diabetes mellitus type I, the recommended daily dose of captopril is 75-100 mg in divided doses. If further decrease in the arterial pressure is desirable, additional antihypertensive agents may be co-administered.

Renal impairment : Due to the fact that captopril is eliminated mainly through the kidneys, the dosage should be reduced or the time intervals between the doses should be increased in patients with renal impairment. When a concomitant treatment with diuretics is co-administered, the administration of a loop diuretic is preferred (for example, furosemide), instead of a thiazide diuretic, in patients with severe renal impairment. In patients with renal impairment, the following dose regimens are recommended, in order to avoid the accumulation of captopril.

Creatinine clearance (ml/min/1.73 m^2)	Daily starting 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 it also occurs with the other antihypertensive drugs as well, the possibility of commencing treatment with a lower initiating dose should be considered (6.25 mg twice daily) in elderly patients, who may have a reduced renal function or a dysfunction of other organs.
Dosage should be titrated depending on the response of the arterial pressure to treatment and should be maintained at the lowest possible levels that are required for the sufficient control of the arterial pressure.

Children and adolescents: The efficacy and safety of captopril have not been fully evaluated. The administration of captopril to children and adolescents should commence under strict medical surveillance. The initial dose of captopril is approximately 0.3 mg /kg of body weight. In patients for whom special precautions are required (children with renal dysfunction, premature infants, new-borns and infants, whose renal function is not the same as that of older children and adults), the commencing dose should be only 0.15 mg captopril / kg of body weight. In general, captopril is administered to children 3 times a day, nevertheless, the dose and the intervals between doses should be individualized according to the patient's response.

2.7 Overdosage - Treatment
The symptoms of overdose are severe hypotension, shock, lethargy, bradycardia, electrolyte disorders and renal insufficiency.
In case the ingestion of the drug is recent, measures should be taken to prevent the drug's absorption, (such as gastric lavage, administration of absorptive substances and sodium sulphate within 30 min after the ingestion), as well as to accelerate the drug's elimination.
In every case of excessive intake of the drug, please contact your doctor immediately or go to the nearest hospital.

2.8 Undesirable effects
All drugs may cause undesirable effects.
The undesirable effects that have been reported by treatment with captopril or / and the ACE inhibitors include:
Blood and lymphatic system disorders:
Very rare: neutropenia/agranulocytosis, pancytopenia especially in patients with renal dysfunction, anaemia (including aplastic and haemolytic anaemia), thrombocytopenia, lymphadenopathy, eosinophilia, autoimmune diseases and / or a positive ANA-titre).
Disorders of metabolism and nutrition:
Rare: anorexia
Very rare: hyperkalaemia, hypoglycaemia.
Psychiatric disorders:
Common: sleep disorders
Very rare: confusion, depression.
Nervous system disorders:
Common: taste distortion, dizziness.
Rare: nystagmus, headache, and paresthesias.
Very rare: cerebrovascular episodes, including stroke and syncope.
Eye disorders:

Very rare: blurred vision.
Heart disorders:
Uncommon: tachycardia or tachyarrythmia, angina pectoris, palpitations.
Very rare: cardiac arrest, cardiogenic shock.
Vascular disorders:
Uncommon: hypotension, Raynaud syndrome, flush, paleness.
Respiratory, thoracic and mediastinal disorders :
Common: dry, irritating (non-productive) cough and dyspnoea.
Very rare: bronchospasm, rhinitis, allergic alveolitis/eosinophilic pneumonia.
Gastrointestinal disorders :
Common: nausea, vomiting, stomach irritation, abdominal pain, diarrhoea, constipation, dry mouth.
Rare: stomatitis/aphthous ulcerations
Very rare: glossitis, peptic ulcer, pancreatitis.
Hepato-biliary disorders :
Very rare : reduced hepatic function and cholestasis (including jaundice), hepatitis including also necrosis, increased levels of liver enzymes and of bilirubin.
Disorders of the skin and subcutaneous tissue:
Common: itching with or without a rash, rash and alopecia.
Uncommon: angioedema
Very rare : urticaria, Stevens Johnson Syndrome, erythema multiforme, light-sensitivity, erythroderma, pemphigoid reactions, exfoliative dermatitis.
Musculoskeletal disorders, disorders of the connective tissues and of the bones:
Very rare : myalgia, arthralgia
Renal and urinary disorders:
Rare : disorders of the renal function, including also renal insufficiency, polyuria, oliguria, increased urine frequency.
Very rare : nephrotic syndrome.
Reproductive system and breast disorders:
Very rare : incompetence, gynaecomastia.
General disorders:
Uncommon: chest pain, sense of fatigue, malaise.
Very rare: fever.
Investigations:
Very rare: proteinuria, eosinophilia, increase in the serum levels of potassium, reduction in the serum levels of sodium, increase in urea, in serum creatinine and serum bilirubin, reduction in haemoglobin, hematocrit, leucocytes, thrombocytes, positive ANA titre, increased erythrocyte sedimentation rate (ESR).

2.9 What the patient should know in case he/she missed a dose
If by chance a dose is missed, you should take the dose as soon as possible. If however the time approaches for the administration of the next dose, do not take the missed dose but continue your therapy normally. Do not double the doses.

2.10 What the patient should know for the expiry date of the medicinal product
Do not use NORMOLOSE after the expiry date written on the inner and outer package.

2.11 Special precautions for the storage of the medicinal product
Keep at temperature below 25^{o}C in a dry place, protected from light, out of reach and sight of children.

2.12 Date of last revision of the Patient Information Leaflet
05/2012

3. INFORMATION ON THE PROPER USE OF DRUGS

- This drug was prescribed to you by your doctor only for your specific medical problem. It should not be given to other persons or be used for any other disease, without having previously asked for your doctor's advice.
- If during therapy a problem occurs with the drug, inform your doctor or pharmacist.
- If there are any questions concerning the information of the drug that you receive, or you need to be better informed on your medical problem, do not hesitate to ask for this information from your doctor or pharmacist.
- In order for your drug to be effective and safe, this drug should be taken according to the instructions given to you.
- For your safety and health it is necessary for you to read with caution the information regarding the drug given to you.
- Do not keep any medication in the bathroom shelves, because heat and moisture may spoil them and render them harmful for your health.
- Do not keep drugs you no longer need or that have already expired.
- Keep all drugs out of the sight and reach of children.

4. DRUG AVAILABILITY

Medicinal Product subject to medical prescription (POM).

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