

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Captopril 12.5mg Tablets and or Ecopace 12.5mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Captopril Tablet 12.5mg contains Captopril BP 12.5mg

3. PHARMACEUTICAL FORM

Uncoated Tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hypertension: Captopril is indicated for the first line treatment of mild to moderate hypertension. In severe hypertension it should be used where standard therapy is ineffective or inappropriate.

Congestive Heart Failure : Captopril is indicated for the treatment of congestive heart failure. The drug should be used together with diuretics and, where appropriate, digitalis.

Myocardial Infarction: Captopril is indicated following myocardial infarction in clinically stable patients with asymptomatic and symptomatic left ventricular dysfunction to improve survival, delay the onset of symptomatic heart failure, reduce hospitalisations for heart failure, and reduce recurrent myocardial infarction and coronary revascularisation procedures.

Determination of cardiac function by radionuclide ventriculography or echocardiography should be undertaken prior to initiation of preventative treatment with Captopril in post myocardial infarction patients.

4.2. Posology and method of administration

For oral administration only

Hypertension: Treatment with Captopril should be started at the lowest effective dose and titrated to the individual according to their needs.

Mild to moderate hypertension: The starting dose is 12.5mg twice daily. The usual maintenance dose is 25mg twice daily, which can be increased incrementally every 14 to 28 days until a satisfactory response has been achieved, to a maximum dose of 50mg twice daily.

A thiazide diuretic may be added to Captopril if a satisfactory response has not been achieved. The dose of diuretic may be increased at 1-2 week intervals to the level of optimum response or until the maximum dose is reached.

Severe hypertension: In severe hypertension where standard therapy is ineffective or inappropriate because of adverse effects, the starting dose is 12.5mg twice daily. This may be increased incrementally up to a maximum of 50mg three times a day. Captopril should be used together with other anti-hypertensive agents but the dose of these should be individually titrated. A daily dose of 150mg Captopril should not normally be exceeded.

Heart failure: Captopril therapy must be started under close medical supervision. Captopril should be introduced when diuretic therapy (such as frusemide 40-80mg or equivalent) is insufficient to control symptoms. A starting dose of 6.25mg or 12.5mg may minimise a transient hypotensive effect. The possibility of this occurring can be reduced by discontinuing or reducing diuretic therapy if possible, prior to Initiating Captopril. The usual maintenance dose is 25mg, two or three times a day which can be increased incrementally, with intervals of at least 14 days, until a satisfactory response is achieved. The usual maximum dose is 150mg daily.

Myocardial infarction: Therapy may be initiated as early as three days following a myocardial infarction. After an initial dose of 6.25mg, Captopril therapy should be titrated to a final target dose of 150mg daily in divided doses over the next several weeks. Achievement of the target dose of 150mg should be based on the patient's tolerance to Captopril during titration.

If symptomatic hypotension occurs, a dosage reduction may be required. Captopril may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, aspirin and beta-blockers.

Elderly: The dose should be titrated against the blood pressure response and kept as low as possible to achieve adequate control. Since elderly patients may have reduced renal function and other organ dysfunctions, it is suggested that a low dose of Captopril be used initially.

Children: Captopril is not recommended for the treatment of mild to moderate hypertension in children. Experience in neonates, particularly premature infants, is limited. Because renal function in infants is not equivalent to that of older children and adults, lower doses of Captopril should be used with patients under close medical supervision.

The starting dose should be 0.3mg per kg bodyweight up to a maximum of 6mg per kg bodyweight daily in divided doses. The dose should be

individualised according to the response and may be given two to three times daily.

Patients with renal impairment: Captopril in divided doses of 75 to 100mg/day was well tolerated in patients with diabetic nephropathy and mild to moderate renal impairment (creatinine clearance at least 30 ml/min/1.73m²). Patients with severely impaired renal function will take longer to reach steady state Captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. These patients may therefore respond to smaller or less frequent doses.

Therefore, in patients with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m²), the initial daily dose should be 12.5mg bd. The dose can then be titrated against the response but adequate time should be allowed between dosage adjustments. When concomitant diuretic therapy is required, a loop diuretic rather than a thiazide diuretic should be the diuretic of choice.

Captopril is readily eliminated by haemodialysis.

4.3. Contraindications

Hypersensitivity to ACE inhibitors or any of the constituents of the product.

Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary / idiopathic angioneurotic oedema.
- Lactation (see 4.6).

4.4. Special warnings and precautions for use

Angioedema: angioedema of the extremities, face, lips, mucous membranes, tongue, glottis or larynx may occur in patients treated with ACE inhibitors particularly during the first weeks of treatment. However, in rare cases, severe angioedema may develop after long-term treatment with an ACE inhibitor. Treatment should be discontinued promptly. Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be instituted. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

As limited experience has been obtained in the treatment of acute hypertensive crises, the use of Captopril should be avoided in these patients.

Aortic and mitral valve stenosis/Obstructive hypertropic cardiomyopathy: Captopril should not be used in patients with aortic stenosis or outflow tract

obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal impairment:

Adverse reactions to Captopril are principally associated with renal function since the drug is mainly excreted by the kidneys.

In cases of renal impairment (creatinine clearance < 40 ml/min), the initial dosage of captopril must be adjusted according to the patient's creatinine clearance (see 4.2), and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.

Hypotension: With the first one or two doses some patients may experience symptomatic hypotension. In most cases, symptoms are relieved simply by lying the patient down. In patients with severe congestive heart failure, who are receiving large doses of diuretic, exaggerated hypotensive responses have occurred, usually within one hour of the initial dose of Captopril. In these patients, by discontinuing diuretic therapy, or significantly reducing the diuretic dose for 4 to 7 days prior to initiating Captopril the possibility of this occurrence is reduced. By commencing Captopril therapy with small doses (6.25 or 12.5mg) the duration of any hypotensive effect is lessened.

The occurrence of first dose hypotension does not preclude subsequent dose titration with Captopril.

Hypotension has been occasionally reported in patients on Captopril due to causes of acute volume depletion such as vomiting and diarrhoea.

As with any antihypertensive agent, excessive blood pressure lowering in patients with ischaemic cardiovascular or cerebrovascular disease may increase the risk of myocardial infarction or stroke. Volume repletion with intravenous normal saline may be required.

Renovascular hypertension: Some patients with renal disease, particularly those with bilateral renal artery stenosis or unilateral renal artery stenosis in a single functioning kidney, have developed increased concentrations of blood urea and serum creatinine.

Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients it may not be possible to normalise blood pressure and maintain adequate renal perfusion.

Cough: cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy.

Hyperkalaemia: elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those

patients taking other drugs associated with increases in serum potassium (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 captopril is not recommended (see 4.5)

Proteinuria: proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Total urinary proteins greater than 1 g per day were seen in about 0.7% of patients receiving captopril. The majority of patients had evidence of prior renal disease or had received relatively high doses of captopril (in excess of 150 mg/day), or both. Nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Patients with prior renal disease should have urinary protein estimations (dipstick on first morning urine) prior to treatment, and periodically thereafter.

Anaphylactoid reactions during desensitisation: sustained life-threatening anaphylactoid reactions have been rarely reported for patients undergoing desensitising treatment with hymenoptera venom while receiving another ACE inhibitor. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Anaphylactoid reactions during high-flux dialysis / lipoprotein apheresis membrane exposure:

Recent clinical observations have shown a high incidence of anaphylactoidlike reactions during haemodialysis with high-flux dialysis membranes (e.g. AN69) in patients receiving ACE inhibitors. Therefore, this combination should be avoided.

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

Haematological: Neutropenia/agranulocytosis thrombocytopenia and anaemia have been reported in patients receiving Captopril.

In patients with normal renal function and no other complicating factors, neutropenia occurs rarely.

Captopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with Allopurinol or

Procainamide, or a combination of these complicating factors. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy.

If Captopril is used in such patients, it is advised that white blood cell count and differential counts should be performed prior to therapy, every 2 weeks during the first three months of Captopril therapy, and periodically thereafter.

During treatment, all patients should be instructed to report any sign of infection (e.g. sore throat, fever), when a differential white blood cell count should be performed. Captopril and other concomitant medication should be withdrawn if neutropenia (neutrophils less than 1000/mm³) is detected or suspected. In most patients neutrophil counts rapidly returned to normal upon discontinuing Captopril.

Surgery / anaesthesia: In patients undergoing major surgery, or during anaesthesia with agents which produce hypotension, Captopril will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

Diabetic patients: the glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.

Lactose: Captopril contains lactose, therefore it should not be used in cases of congenital galactosaemia, glucose and galactose malabsorption or lactase deficiency syndromes (rare metabolic diseases).

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

Pregnancy: ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

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

Diuretics (thiazide or loop diuretics): prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with captopril (see 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of captopril. However, no clinically significant drug interactions have been found in specific studies with hydrochlorothiazide or furosemide.

Other antihypertensive agents: Captopril has been safely co-administered with other commonly used anti-hypertensive agents (e.g. moxonidine, alpha-blockers, beta-blockers MAOIs, Tricyclic antidepressants and long-acting calcium channel blockers). Concomitant use of these agents may increase the hypotensive effects of captopril. Treatment with nitroglycerine and other nitrates, or other vasodilators such as minoxidil, should be used with caution.

Clonidine: It has been suggested that the anti-hypertensive effect of Captopril can be delayed when patients treated with clonidine are changed to Captopril.

Treatments of acute myocardial infarction: captopril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates in patients with myocardial infarction.

Tricyclic antidepressants / Antipsychotics: ACE inhibitors may enhance the hypotensive effects of certain tricyclic antidepressants and antipsychotics (see 4.4). Postural hypotension may occur

Non-steroidal anti-inflammatory medicinal products: it has been described that non-steroidal anti-inflammatory medicinal products (NSAIDs) and ACE inhibitors exert an additive effect on the increase in serum potassium whereas renal function may decrease. These effects are, in principle, reversible. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated. Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor.

Allopurinol and Procainamide: There have been reports of neutropenia and/or Stevens-Johnson syndrome in patients on Captopril plus either Allopurinol or procainamide. Although a causal relationship has not been established, these combinations should only be used with caution, especially in patients with impaired renal function.

Immunosuppressants: Azathioprine and Cyclophosphamide have been associated with blood dyscrasias in patients with renal failure who were also taking Captopril.

Ciclosporin: increased risk of hyperkalaemia when ACE inhibitors given with ciclosporin.

Probenecid: The renal clearance of Captopril is reduced in the presence of Probenecid.

Lithium: reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of captopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see 4.4)

Sympathomimetics: may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored.

Antidiabetics: pharmacological studies have shown that ACE inhibitors, including captopril, can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics such as sulphonylurea in diabetics. Should this very rare interaction occur, it may be necessary to reduce the dose of the antidiabetic during simultaneous treatment with ACE inhibitors.

Enhanced hypotensive effect when ACE inhibitors given with following drugs:

Tizanidine, Baclofen, Anxiolytics and Hypnotics, Sodium Nitroprusside, Anaesthetics(general), Alprostadil, Aldesleukin, Moxonidine, Moxisylyte(thymoxamine), Levodopa, Diazoxide, Alcohol

Increased risk of hyperkalaemia when ACE inhibitors given with following: Angiotensin-II Receptor Antagonists.

Digoxin: captopril possibly increases plasma concentration of digoxin.

Clinical chemistry: Captopril may cause a false- positive urine test for acetone.

4.6. Pregnancy and lactation

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

Pregnancy:

When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but limited number of cases of first trimester exposures have not shown malformations

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose

mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation:

Captopril is contraindicated in the lactation period.

Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of Captopril tablets in breastfeeding is not recommended for infants, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.

4.7. Effects on ability to drive and use machines

As with other antihypertensives, the ability to drive and use machines may be reduced, namely at the start of the treatment, or when posology is modified, and also when used in combination with alcohol, but these effects depend on the individual's susceptibility.

4.8. Undesirable effects

Undesirable effects reported for captopril and/or ACE inhibitor therapy include:

Blood and lymphatic disorders:

very rare: neutropenia/agranulocytosis (see 4.4), pancytopenia particularly in patients with renal dysfunction (see 4.4), anaemia (including aplastic and haemolytic), thrombocytopenia, lymphadenopathy, eosinophilia, auto-immune diseases and/or positive ANA-titres.

Metabolism and nutrition disorders:

rare: anorexia

very rare: hyperkalaemia, hypoglycaemia (see 4.4)

Psychiatric disorders:

common: sleep disorders

very rare: confusion, depression.

Nervous system disorders:

common: taste impairment, dizziness

rare: drowsiness, headache and paraesthesia

very rare: cerebrovascular incidents, including stroke, and syncope.

Eye disorders:

very rare: blurred vision

Cardiac disorders:

uncommon: tachycardia or tachyarrhythmia, angina pectoris, palpitations.

very rare: cardiac arrest, cardiogenic shock

Vascular disorders:

uncommon: hypotension (see 4.4), Raynaud syndrome, flush, pallor

Respiratory, thoracic and mediastinal disorders:

common: dry, irritating (non-productive) cough (see 4.4) and dyspnoea

very rare: bronchospasm, rhinitis, allergic alveolitis / eosinophilic pneumonia

Gastrointestinal disorders:

common: nausea, vomiting, gastric irritations, abdominal pain, diarrhoea, constipation, dry mouth.

rare: stomatitis/aphthous ulcerations

very rare: glossitis, peptic ulcer, pancreatitis.

Hepato-biliary disorders:

very rare: impaired hepatic function and cholestasis (including jaundice), hepatitis including necrosis, elevated liver enzymes and bilirubin.

Skin and subcutaneous tissue disorders:

common: pruritus with or without a rash, rash, and alopecia.

uncommon: angioedema (see 4.4)

very rare: urticaria, Stevens Johnson syndrome, erythema multiforme, photosensitivity, erythroderma, pemphigoid reactions and exfoliative dermatitis.

Musculoskeletal, connective tissue and bone disorders:

very rare: myalgia, arthralgia.

Renal and urinary disorders:

rare: renal function disorders including renal failure, polyuria, oliguria, increased urine frequency.

very rare: nephrotic syndrome.

Reproductive system and breast disorders:

very rare: impotence, gynaecomastia.

General disorders:

uncommon: chest pain, fatigue, malaise

very rare: fever

Investigations:

very rare: proteinuria, eosinophilia, increase of serum potassium, decrease of serum sodium, elevation of BUN, serum creatinine and serum bilirubin, decreases in haemoglobin, haematocrit, leucocytes, thrombocytes, positive ANA-titre, elevated ESR.

4.9 Overdose

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure.

Treatment:

The use of activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) should be considered if the patient presents within 1 hour of ingestion of a potentially toxic amount (5mg/ kg for adults and children). Monitor BP, pulse and perform 12 lead ECG. Measure U&Es and creatinine. Consider blood gas analysis in symptomatic patients. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementations should be given rapidly. Where hypotension is thought mainly due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as noradrenaline or high dose dopamine may be beneficial. The dose of vasopressor should be titrated against blood pressure.

Captopril may be removed from circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES**5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: ACE inhibitors, plain, ATC code: C09AA01

Captopril is a highly specific, competitive inhibitor of angiotensin-I converting enzyme (ACE inhibitors).

The beneficial effects of ACE inhibitors appear to result primarily from the suppression of the plasma renin-angiotensin-aldosterone system. Renin is an endogenous enzyme synthesised by the kidneys and released into the circulation where it converts angiotensinogen to angiotensin-I a relatively inactive decapeptide. Angiotensin-I is then converted by angiotensin converting enzyme, a peptidyl dipeptidase, to angiotensin-II. Angiotensin-II is a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure, as well as for stimulation of the adrenal gland to secrete aldosterone. Inhibition of ACE results in decreased plasma angiotensin-II, which leads to decreased vasopressor activity and to reduced aldosterone secretion. Although the latter decrease is small, small increases in serum potassium concentrations may occur, along with sodium and fluid loss. The cessation of the negative feedback of angiotensin-II on the renin secretion results in an increase of the plasma renin activity.

Another function of the converting enzyme is to degrade the potent vasodepressive kinin peptide bradykinin to inactive metabolites. Therefore, inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin-system which contributes to peripheral vasodilation by activating the prostaglandin system; it is possible that this mechanism is involved in the hypotensive effect of ACE inhibitors and is responsible for certain adverse reactions.

Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of captopril. The duration of effect is dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The

blood pressure lowering effects of captopril and thiazide-type diuretics are additive.

In patients with hypertension, captopril causes a reduction in supine and erect blood pressure, without inducing any compensatory increase in heart rate, nor water and sodium retention.

In haemodynamic investigations, captopril caused a marked reduction in peripheral arterial resistance. In general there were no clinically relevant changes in renal plasma flow or glomerular filtration rate. In most patients, the antihypertensive effect began about 15 to 30 minutes after oral administration of captopril; the peak effect was achieved after 60 to 90 minutes. The maximum reduction in blood pressure of a defined captopril dose was generally visible after three to four weeks.

In the recommended daily dose, the antihypertensive effect persists even during long-term treatment. Temporary withdrawal of captopril does not cause any rapid, excessive increase in blood pressure (rebound). The treatment of hypertension with captopril leads also to a decrease in left ventricular hypertrophy.

Haemodynamic investigations in patients with heart failure, showed that captopril caused a reduction in peripheral systemic resistance and a rise in venous capacity. This resulted in a reduction in pre-load and after-load of the heart (reduction in ventricular filling pressure). In addition, rises in cardiac output, work index and exercise capacity have been observed during treatment with captopril. In a large, placebo-controlled study in patients with left ventricular dysfunction (LVEF < 40%) following myocardial infarction, it was shown that captopril (initiated between the 3rd to the 16th day after infarction) prolonged the survival time and reduced cardiovascular mortality. The latter was manifested as a delay in the development of symptomatic heart failure and a reduction in the necessity for hospitalisation due to heart failure compared to placebo. There was also a reduction in re-infarction and in cardiac revascularisation procedures and/or in the need for additional medication with diuretics and/or digitalis or an increase in their dosage compared to placebo.

A retrospective analysis showed that captopril reduced recurrent infarcts and cardiac revascularisation procedures (neither were target criteria of the study). Another large, placebo-controlled study in patients with myocardial infarction showed that captopril (given within 24 hours of the event and for a duration of one month) significantly reduced overall mortality after 5 weeks compared to placebo. The favourable effect of captopril on total mortality was still detectable even after one year. No indication of a negative effect in relation to early mortality on the first day of treatment was found.

Captopril cardioprotection effects are observed regardless of the patient's age or gender, location of the infarction and concomitant treatments with proven efficacy during the postinfarction period (thrombolytic agents, beta-blockers and acetylsalicylic acid).

Type I diabetic nephropathy

In a placebo-controlled, multicentre double blind clinical trial in insulin-dependent (Type I) diabetes with proteinuria, with or without hypertension (simultaneous administration of other antihypertensives to control blood pressure was allowed), captopril significantly reduced (by 51%) the time to doubling of the baseline creatinine concentration compared to placebo; the incidence of terminal renal failure (dialysis, transplantation) or death was also significantly less common under captopril than under placebo (51%). In patients with diabetes and microalbuminuria, treatment with captopril reduced albumin excretion within two years.

The effects of treatment with captopril on the preservation of renal function are in addition to any benefit that may have been derived from the reduction in blood pressure.

5.2. Pharmacokinetic properties

Captopril is administered two or three times a day about one or two hours before meals. At two to four week intervals doses can be increased until blood pressure is controlled or up to a maximum dose of 150mg per day in divided doses. Beyond this dose there is no further therapeutic benefit.

Because Captopril is mainly excreted by the kidney care must be taken in patients with renal insufficiency where the dose must be titrated with the blood pressure response.

Lactation:

In the report of twelve women taking oral captopril 100 mg 3 times daily, the average peak milk level was 4.7 µg/L and occurred 3.8 hours after the dose. Based on these data, the maximum daily dosage that a nursing infant would receive is less than 0.002% of the maternal daily dosage.

5.3. Preclinical safety data

Captopril is an established drug with a well known pre-clinical profile.

Captopril has been shown to be lethal to rabbit and sheep foetuses. There were no foetotoxic effects to rabbit and hamster foetuses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose D.C. Ph.Eur.
Maize Starch D.C. Ph.Eur.
Microcrystalline Cellulose Ph.Eur.
Stearic Acid BP.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Captopril tablets have a shelf-life of 3 years.

6.4. Special precautions for storage

Store at a temperature not exceeding 25°C.

6.5. Nature and contents of container

Captopril 25mg tablets are available Calendar-packed in strips of 14, in packs of 56.

6.6. Instructions for use/handling

No special precautions.

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited,
NLA Tower,
12-16 Addiscombe Road,
Croydon,
CR0 0XT,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER

PL 12762/0001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF
AUTHORISATION**

10 DATE OF REVISION OF THE TEXT

19/10/2010