

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0577/024/001

Case No: 2062133

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDermott Laboratories Ltd t/a Gerard Laboratories

35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Geroten, 12.5 Milligram

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **24/02/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Geroten Tablets 12.5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 12.5mg Captopril.
Also contains 12.5mg anhydrous lactose.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, elongated tablet with partial bisect and 'G' on one side and partial bisect and 'C 12.5' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension: Captopril is indicated for the treatment of hypertension.

Heart Failure: Captopril is indicated for the treatment of chronic heart failure with reduction of systolic ventricular function, in combination with diuretics and, when appropriate, digitalis and beta-blockers.

Myocardial Infarction:

- *Short-term (4 weeks) treatment:* Captopril is indicated in any clinically stable patient within the first 24 hours of an infarction.
- *Long-term prevention of symptomatic heart failure:* Captopril is indicated in clinically stable patients with asymptomatic left ventricular dysfunction (ejection fraction \leq 40%).

Type I Diabetic Nephropathy: Captopril is indicated for the treatment of macroproteinuric diabetic nephropathy in patients with type I diabetes. (See section 5.1).

4.2 Posology and method of administration

Dose should be individualised according to patient's profile (see 4.4) and blood pressure response.

The recommended maximum daily dose is 150 mg.

Captopril may be taken before, during and after meals.

Hypertension: the recommended starting dose is 25 – 50mg daily in two daily doses. The dose may be increased incrementally, with intervals of at least 2 weeks, to 100 – 150 mg/day in two divided doses as needed to reach target blood pressure. Captopril may be used alone or with other antihypertensive agents, especially thiazide diuretics. A once-daily dosing regimen may be appropriate when concomitant antihypertensive medication such as thiazide diuretics is added. In patients with a strongly active renin-angiotensin-aldosterone system (hypovolaemia, renovascular hypertension, cardiac decompensation) it is preferable to commence with a single dose of 6.25mg or 12.5mg. The inauguration of this treatment should preferably take place under close medical supervision. These doses will then be administered at a rate of two per day. The dosage can be gradually increased to 50mg per day in one or two doses and if

necessary to 100mg per day in one or two doses.

Heart Failure: treatment with captopril for heart failure should be initiated under close medical supervision. The usual starting dose is 6.25mg – 12.5mg BID or TID. Titration to the maintenance dose (75 – 150 mg per day) should be carried out based on patient's response, clinical status, and tolerability, up to a maximum of 150mg per day in divided doses. The dose should be increased incrementally, with intervals of at least 2 weeks to evaluate patient's response.

Myocardial Infarction:

Short term treatment: Captopril treatment should begin in hospital as soon as possible following the appearance of the signs and/ or symptoms in patients with stable haemodynamics. A 6.25mg test dose should be administered, with a 12.5mg dose being administered 2 hours afterwards and a 25mg dose 12 hours later.

From the following day, captopril should be administered in a 100mg/day dose, in two daily administrations, for 4 weeks, if warranted by the absence of adverse haemodynamic reactions. At the end of the 4 week treatment, the patient's state should be reassessed before a decision is taken concerning treatment for the post-myocardial infarction stage.

Chronic treatment: if captopril treatment has not begun during the first 24 hours of the acute myocardial infarction stage, it is suggested that treatment be instigated between the 3rd and 16th day post-infarction once the necessary treatment conditions have been attained (stable haemodynamics and management of any residual ischaemia).

Treatment should be started in hospital under strict surveillance (particularly of blood pressure) until the 75mg dose is reached. The initial dose must be low (see 4.4), particularly if the patient exhibits normal or low blood pressure at the initiation of therapy. Treatment should be initiated with a dose of 6.25mg followed by 12.5mg 3 times daily for 2 days and then 25mg 3 times daily if warranted by the absence of adverse haemodynamic reactions. The recommended dose for effective cardioprotection during long term treatment is 75mg to 150mg daily in two or three doses. In cases of symptomatic hypotension, as in heart failure, the dose of diuretics and/or other concomitant vasodilators may be reduced in order to attain the steady-state dose of captopril. When necessary, the dose of captopril should be adjusted in accordance with patient's clinical reactions. Captopril may be used in combination with other treatments for myocardial infarction such as thrombolytic agents, beta-blockers and acetylsalicylic acid.

Type I Diabetic Nephropathy: in patients with type I diabetic nephropathy, the recommended daily dose of captopril is 75 – 100mg in divided doses. If additional lowering of blood pressure is desired, additional antihypertensive medications may be added.

Renal Impairment: since captopril is excreted primarily via the kidneys, dosage should be reduced or the dosage interval should be increased in patients with impaired renal function. When concomitant diuretic therapy is required a loop diuretic (e.g. furosemide), rather than a thiazide diuretic, is preferred in patients with severe renal impairment. In patients with impaired renal function, the following daily dose may be recommended to avoid accumulation of captopril.

Creatinine Clearance (ml/min/1.73m ²)	Daily starting dose (mg)	Daily maximum 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 agents, consideration should be given to initiating therapy with a lower starting dose (6.25 mg BID) in elderly patients who may have reduced renal function and other organ dysfunctions (see above and section 4.4)

Dosage should be titrated against the blood pressure response and kept as low as possible to achieve adequate control.

Children and adolescents: the efficacy and safety of captopril have not been fully established. The use of captopril in children and adolescents should be initiated under close medical supervision. The initial dose of captopril is about 0.3mg/kg body weight. For patients requiring special precautions (children with renal dysfunction, premature infants,

new-borns and infants, because their renal function is not the same with older children and adults) the starting dose should be only 0.15mg captopril/kg weight.

Generally, captopril is administered to children 3 times a day, but dose and interval of dose should be adapted individually according to patient's response.

4.3 Contraindications

- History of hypersensitivity to captopril, to any of the excipients or any other ACE inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary/ idopathic angioneurotic oedema.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Hypotension: rarely hypotension is observed in uncomplicated hypertensive patients.

Symptomatic hypotension is more likely to occur in hypertensive patients who are volume and/ or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, vomiting, or haemodialysis. Volume and/ or sodium depletion should be corrected before the administration of an ACE inhibitor and a lower starting dose should be considered.

Patients with heart failure are at higher risk of hypotension and a lower starting dose is recommended when initiating therapy with an ACE inhibitor. Caution should be used whenever the dose of captopril or diuretic is increased in patients with heart failure.

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. If hypotension develops, the patient should be placed in a supine position. Volume repletion with intravenous normal saline may be required.

Renovascular hypertension: there is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration and monitoring of renal function.

Renal impairment: 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.

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 hospitalized and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

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

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.

Hyperkalaemia: evaluations 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).

Aortic and mitral value stenosis/ Obstructive hypertrophic cardiomyopathy: ACE inhibitors should be used with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Neutropenia/ Agranulocytosis: neutropenia/ agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, including 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, especially if there is pre-existing impaired renal function. 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 3 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 (see 4.5) should be withdrawn if neutropenia (neutrophils less than $1000/\text{mm}^3$) is detected or suspected. In most patients neutrophil counts rapidly return to normal on discontinuing captopril.

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 patients with proteinuria.

Patients with prior renal disease should have urinary protein estimations (dip-stick 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: anaphylactoid reactions have been reported in patients haemodialysed with high-flux dialysis membranes or undergoing low-density lipoprotein apheresis with dextran sulphate absorption. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication.

Surgery / Anaesthesia: hypotension may occur in patients undergoing major surgery or during treatment with anaesthetic agents that are known to lower blood pressure. If hypotension occurs, it may 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 increased 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 of 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 antihypertensive agents (e.g. beta-blockers 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, should be used with caution.

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.

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)

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

Allopurinol, procainamide, cytostatic or immunosuppressive agents: concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia especially when the latter are used at higher than currently recommended doses.

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, where as 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.

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.

Clinical Chemistry

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

4.6 Pregnancy and lactation**Pregnancy:**

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).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. 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.

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:

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 Geroten in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.

In the case of an older infant, the use of Geroten in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

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 treatment, or when the posology is modified, 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, photo-sensitivity, 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.

Measures to prevent absorption (e.g. gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake) and hasten elimination should be applied if ingestion is recent.

If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin-II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. 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 kidney 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 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 \leq 40%) following myocardial infarction, it was shown that captopril (initiated between the 3rd and 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 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 of gender, location of the infarction and concomitant treatments with proven efficacy during the post-infarction period (thrombolytic agent, 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 an orally active agent that does not require biotransformation for activity. The average minimal absorption is approximately 75%. Peak plasma concentrations are reached within 60-90 minutes. The presence of food in the gastrointestinal tract reduces absorption by about 30-40%. Approximately 25-30% of the circulating drug is bound to plasma proteins.

The apparent elimination half-life of unchanged captopril in blood is about 2 hours. Greater than 95% of the absorbed dose is eliminated in the urine within 24 hours; 40-50% is unchanged drug and the remainder are inactive disulphide metabolites (captopril disulphide and captopril cysteine disulphide). Impaired renal function could result in drug accumulation. Therefore, in patients with impaired renal function the dose should be reduced and/ or dosage interval prolonged (see 4.2).

Studies in animals indicate that captopril does not cross the blood-brain barrier to any significant extent.

Lactation:

In the report of twelve women taking oral captopril 100 mg 3 times daily, the average peak milk level was 4.7µg/L and occurred 3.8 hours after the dose. Based on this 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

Animal studies performed during organogenesis with captopril have not shown any teratogenic effect but captopril has produced foetal toxicity in several species, including foetal mortality during late pregnancy, growth retardation and postnatal mortality in the rat. Preclinical data reveal no other specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Lactose Anhydrous
Maize Starch
Stearic Acid
Sodium Starch Glycolate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Blister: 3 years
HDPE Bottle: 3 years
Polypropylene Pot: 2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package or container.

6.5 Nature and contents of container

Blister, HDPE bottle, polypropylene pot.
28, 30, 56, 60, 84, or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd
trading as:
Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA 577/24/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th December 1996

Date of last renewal: 13th December 2006

10 DATE OF REVISION OF THE TEXT

February 2009