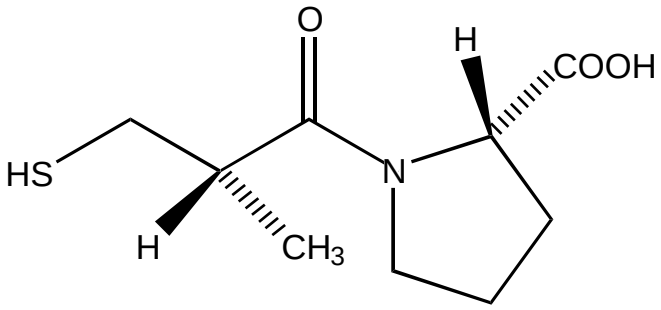
TERRY WHITE CHEMISTS CAPTOPRIL TABLETS

NAME OF THE MEDICINE

Captopril.

Chemical Name: 1-[(2s)-3-mercapto-2-methylpropionyl]-L-proline.

Chemical Structure:



Molecular Formula: $C_9H_{15}NO_3S$.

Molecular Weight: 217.3.

CAS Registry Number: 62571-86-2.

DESCRIPTION

Captopril is a white or almost white, crystalline powder. It is soluble in water and in ethanol (96%).

Captopril is the first of a chemical class of anti-hypertensive agents known as the angiotensin converting enzyme (ACE) inhibitors. It is a highly specific competitive inhibitor of angiotensin I converting enzyme, the enzyme responsible for conversion of angiotensin I to angiotensin II. Captopril has also been shown to be of benefit in the management of heart failure.
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PHARMACOLOGY

Mechanism of Action

The mechanism of action of captopril has not yet been fully elucidated; its beneficial effects in hypertension and heart failure appear to result primarily through suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesised by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted enzymatically by angiotensin-converting enzyme (ACE) to the octapeptide angiotensin II, one of the most potent endogenous vasoconstrictor substances. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention and potassium loss.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxyhydrolase. As a result there is a decrease in the pressor substance, angiotensin II, and a subsequent increase in plasma renin activity (PRA). The increase in PRA is due to the relative lack of negative feedback on renin release caused by reduction in angiotensin II. Decreased concentrations of aldosterone are found in blood and urine and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

Captopril may also interfere with the degradation of the vasopressor peptide, bradykinin. ACE is identical to “bradykininase”, an enzyme involved in the degradation of bradykinin. Bradykininase

inhibition may lead to increased concentrations of bradykinin or prostaglandin E2 which may also have a role in the therapeutic effect of captopril.

Pharmacokinetics

Absorption

Following oral administration of captopril, rapid absorption occurs with peak blood levels of approximately 1 µg/mL being found 30 to 60 minutes after a 100 mg dose. The average absorption is approximately 75%. Absorption of captopril is reduced by 25 to 40% when food is present in the gastrointestinal tract.

The apparent oral bioavailability is increased in patients receiving captopril chronically compared with acute use. It may be possible to reduce the dosage during chronic therapy and still maintain adequate blood pressure control.

Distribution

Distribution of captopril in man appears to be between three compartments. The terminal phase volume of distribution (2 L/kg) suggests that captopril is distributed into deep tissues.

Captopril is approximately 30% bound to plasma proteins.

Metabolism

Captopril is extensively metabolised. The major metabolite is captopril dimer (SQ 14,551).

In vitro studies have demonstrated that SQ 14,551 is significantly less active than captopril as an inhibitor of angiotensin converting enzyme.

Elimination

The principal route of excretion of captopril and its metabolites (captopril dimer and conjugates with endogenous thiol compounds e.g. captopril-cysteine) is in the urine. *In vitro* studies suggest that the metabolites are labile and the interconversions may occur *in vivo*. Approximately 40% of an administered dose is excreted unchanged in the urine in 24 hours and 35% as metabolites. Total body clearance of captopril is approximately 0.8 L/kg/h.

Captopril has an elimination half-life of 1 to 2 hours and of total radioactivity is approximately 4 hours. The elimination half-life of captopril increases with decreasing renal function: the elimination rate correlates with creatinine clearance. The half-life for non-renal elimination is 156 hours. Dosage adjustment is required in patients with renal impairment (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics

Administration of captopril results in a reduction in peripheral arterial resistance in hypertensive patients with either no change or an increase in cardiac output.

Clinically significant reductions of blood pressure are often observed 60 to 90 minutes after oral administration of captopril. However, the reduction in blood pressure is usually progressive and to achieve maximal therapeutic effects of a given dosage regimen, several weeks of administration may be required. The duration of effect appears to be dose related.

Blood pressure is lowered in both standing and supine positions. Orthostatic effects and tachycardia are infrequent, occurring most commonly in volumed-depleted patients. No sudden increase in blood pressure after withdrawal of captopril has been observed.

Studies have demonstrated an increase in renal blood flow after administration of captopril. Glomerular filtration rate is usually unchanged. In instances of rapid reduction of long-standing or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, resulting in transient rises in serum creatinine and urea nitrogen. In humans, the renin-angiotensin system plays a role in regulating the glomerular filtration rate when renal perfusion pressure is low. Administration of captopril may result in acute deterioration of glomerular filtration in such patients.

CLINICAL TRIALS

Captopril improved long-term survival and clinical outcome compared to placebo among 2,231 patients with myocardial infarction (MI) who participated in the Survival and Ventricular Enlargement (SAVE) trial. For inclusion in the study – a randomised, double-blind, placebo-controlled, multi-centre trial – patients (age 21–79 years) had to demonstrate left ventricular dysfunction (ejection fraction <40%) without overt heart failure. Specifically, captopril when given 3–16 days (mean 11 days) after myocardial infarction reduced the following: all cause mortality (risk reduction = 19%, p = 0.022); cardiovascular death (risk reduction = 21%, p = 0.017); manifestations of heart failure requiring initiation or augmentation of digitalis and diuretics (risk reduction = 19%, p = 0.008) or requiring the use of ACE inhibitor therapy (risk reduction = 35%, p < 0.001); hospitalisation for heart failure (risk reduction = 20%, p = 0.034); clinical recurrent MI (risk reduction = 25%, p = 0.011); and coronary re-vascularisation procedures [coronary artery bypass graft surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA)] (risk reduction = 24%, p = 0.014).

Potential mechanisms by which captopril improves survival and clinical outcome in patients following myocardial infarction include: attenuation of the progressive left ventricular dilatation and deterioration in left ventricular function; and inhibition of neurohumoral activation.

Heart failure patients treated with captopril demonstrate increases in exercise time, ability to perform at higher workloads and improvement in functional capabilities, as given by the New York Heart Association criteria. Administration of captopril to heart failure patients has resulted in consistent increases in cardiac output, cardiac index and stroke volume index. The effects were accompanied by reductions in systemic vascular resistance, pulmonary vascular resistance, total vascular resistance, pulmonary arterial pressure, pulmonary capillary wedge pressure and right atrial pressure. A consistent fall in mean arterial pressure was generally seen but rarely became symptomatic. After short term administration a slight reduction in heart rate occurred, which generally returned to pre-captopril levels with long term therapy. Occasionally a more marked reduction in heart rate may occur.

In studies involving a small number of patients with heart failure, a reduction in coronary blood flow, which correlated with a fall in myocardial oxygen demand, has been observed with simultaneous increases in cardiac index and reduction in systemic vascular resistance.

In a multicentre, double-blind, placebo-controlled trial among 409 patients with insulin-dependent diabetes mellitus and proteinuria with or without hypertension (conventional anti-hypertensive agents were allowed to achieve blood pressure control), captopril treatment provided a 51% risk reduction in doubling of serum creatinine (≤ 0.01) and a 51% risk reduction for the combined morbidity/mortality endpoint of end-stage renal disease (dialysis or renal transplantation) or death ($p \leq 0.01$).

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.

INDICATIONS

Hypertension

Captopril is indicated for the treatment of hypertension.

Consideration should be given to the risk of neutropenia/agranulocytosis when using captopril (see **PRECAUTIONS**).

Captopril is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of captopril and thiazides are approximately additive.

Myocardial Infarction

Captopril is indicated to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction, manifested as an ejection fraction less than or equal to 40% and to reduce the incidence of overt heart failure, and subsequent hospitalisation for congestive heart failure in these patients. The efficacy data for the use of captopril following myocardial infarction are strongest for initiation of therapy beyond 3 days post-infarct.

Heart Failure

Captopril is indicated for the treatment of heart failure. In symptomatic patients it is recommended that captopril be administered together with a diuretic.

Diabetic Nephropathy

Captopril is indicated for the treatment of diabetic nephropathy in patients with Type 1 insulin-dependent diabetes mellitus.

CONTRAINDICATIONS

Captopril is contraindicated in patients with a history of previous hypersensitivity to captopril.

Captopril is contraindicated in pregnancy (see **PRECAUTIONS**).

Captopril is contraindicated in patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an angiotensin converting enzyme inhibitor.

Terry White Chemists Captopril should not be given to patients who have experienced hypersensitivity to the product or any of its ingredients.

PRECAUTIONS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin converting enzyme is essential for degradation of endogenous bradykinin, patients receiving ACE inhibitors are subject to a variety of adverse reactions.

Effects produced range from relatively mild, e.g. cough (see **PRECAUTIONS**), to serious such as the following:

Head and Neck Angioedema

Severe life-threatening angioedema has been reported rarely with most of the angiotensin enzyme (ACE) inhibitors. The overall incidence is approximately 0.1% or 0.2%. There seems to be no sex difference in the incidence of angioedema or in the predisposition to angioedema in patients with heart failure or hypertension. In the majority of reported cases, the symptoms occurred during the first week of therapy. However, the onset of angioedema may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually the angioedema involves non-pitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes. Angioedema may occur with or without urticaria.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. In such cases, the product should be discontinued promptly and appropriate monitoring instituted to ensure complete resolution of symptoms. In instances when swelling has been confined to the face and lips, the angioedema has generally resolved either without treatment or with antihistamines. Angioedema associated with laryngeal oedema is potentially life-threatening. Where involvement of the tongue, glottis, or larynx is likely to cause airway obstruction appropriate therapy, including adrenaline and oxygen administration, should be carried out promptly or the patient hospitalised. Patients who respond to medical treatment should be observed carefully for a possible re-emergence of symptoms of angioedema.

There are reports where changing the patient over to another ACE inhibitor was followed by recurrence of oedema and others where it was not. Because of the potential severity of this rare event another ACE inhibitor should not be used in patients with a history of angioedema to a drug of this class (see **CONTRAINDICATIONS**).

Intestinal Angioedema

Intestinal angioedema has been reported rarely in patients treated with ACE-inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including CT scans or ultrasound, or at surgery, and symptoms resolved after stopping

the ACE inhibitor. Intestinal angioedema should be included in differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid Reactions during Desensitisation

Two patients undergoing desensitising treatment with hymenoptera venom while receiving another ACE inhibitor, enalapril, sustained life-threatening anaphylactoid reactions. 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 Aphaeresis Membrane Exposure

Patients haemodialysed using high-flux polyacrylonitrile ("AN69") membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. Anaphylactoid reactions have also been reported in patients undergoing low density lipoprotein aphaeresis with dextran sulfate absorption. These combinations should therefore be avoided, either by use of a different class of medication or alternative membranes (e.g. cuprophane or polysulphone PSF for haemodialysis).

Proteinuria

Total urinary proteins greater than 1 g per day were seen in about 0.7% of patients receiving captopril, the majority of whom had prior renal disease, or were receiving relatively high doses (in excess of 150 mg per day), or both. This incidence dropped to 0.06% in mild to moderate hypertensive patients. Changes in renal function (as assessed by blood urea nitrogen and serum creatinine) were infrequent and did not occur in those who had no prior renal disease.

Nephrotic syndrome (hypoalbuminaemia, oedema and proteinuria > 3 g per day) occurred in about one-fifth of the 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.

In a multicentre, double-blind, placebo-controlled trial in 207 patients with diabetic nephropathy and proteinuria (≥ 500 mg per day) receiving captopril at 75 mg/day for a median of 3 years, there was a consistent reduction in proteinuria. It is unknown whether long-term therapy in patients with other types or renal disease would have similar effects.

Patients with prior renal disease or those receiving captopril at doses greater than 150 mg per day should have urinary protein estimations (dip-stick on first morning urine) prior to treatment, and periodically thereafter.

Neutropenia / Agranulocytosis

Neutropenia has occurred in some patients receiving captopril. This has been limited chiefly to those who had pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy, or a combination of these complicating factors.

Neutropenia has been seen in one patient out of over 8,600 exposed in clinical trials in patients with hypertension who have normal renal function (serum creatinine less the 1.6 mg/dL and no collagen vascular disease).

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia was increased. In clinical trials the frequency was about 1 per 500 (over 15 times that for uncomplicated hypertension). In these patients daily doses of captopril were relatively high particularly in view of their diminished renal function. The use of allopurinol concomitantly with captopril has been associated with neutropenia in foreign marketing experience in patients with renal failure.

In patients with collagen vascular disease (e.g. systemic lupus erythematosus, scleroderma), particularly those with co-existing renal impairment, captopril should be prescribed only after an assessment of benefit and risk since neutropenia has occurred in 8 of the 124 patients in clinical trials.

Neutropenia was noted 2 to 13 weeks after captopril therapy had been started and the white blood cell count falling to its nadir over 10 to 30 days. Neutropenia was usually not associated with significant alterations in red blood cell or platelet counts.

Evaluation of white cell counts in the total patient population suggests a possible general, but milder, effect on neutrophils. In most studies, there was a 5 to 10% decrease in leucocyte count over the first eight weeks of treatment. This was not seen in patients on placebo, propranolol or hydrochlorothiazide, although it was on standard triple therapy. The change in white cell count was not progressive. After 12 weeks the effect was no longer apparent in most patients. The significance of these changes in white cell count is uncertain.

White blood cell and differential counts should be performed prior to therapy and at regular intervals thereafter for patients with significantly impaired renal function, collagen vascular disease, or who are receiving immunosuppressant drugs and for patients with pre-existing neutropenia.

All patients receiving captopril should be instructed to report any signs of infection (e.g. sore throat, fever). A complete white blood count should be performed immediately when such a report is made.

In general, neutrophils returned to normal in about 2 weeks after captopril was discontinued. Serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness (concurrent collagen vascular disease, renal failure, heart failure) or on immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.

If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2 week intervals for about three months, then periodically.

Upon confirmation of neutropenia (neutrophil count < 1000/mm^3) the physician should withdraw captopril and closely follow the patient's course since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal.

Hypotension

Hypotension may occur occasionally in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in patients with uncomplicated hypertension but can develop in patients with impaired renal function, in those that are salt/volume depleted because of renovascular disease, diuretic therapy, vomiting or diarrhoea, and in patients undergoing dialysis (see **PRECAUTIONS, Interactions with Other Medicines** and **ADVERSE EFFECTS**).

Transient decreases in mean blood pressure greater than 20% are recorded in about half of the patients in heart failure, where the blood pressure was either normal or low. This transient hypotension may occur after any of the first several doses and is usually well tolerated, producing either no symptoms, or brief mild light headedness, although in rare instances it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6% of patients with heart failure.

Only a few patients with refractory heart failure secondary to a mechanical lesion of the heart have been studied with captopril. Of possible concern in patients with aortic stenosis are the potentially harmful consequences of reduced coronary perfusion secondary to hypotension. Patients treated for severe congestive heart failure should be cautioned to increase their physical activity slowly.

Excessive hypotension has been observed in patients with severe congestive heart failure with or without associated renal insufficiency. This may be associated with syncope, neurological deficits, oliguria and/or progressive azotaemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses (6.25 or 12.5 mg two or three times a day) under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

In patients with whom an excessive fall in flood pressure could result in myocardial infarction or cerebrovascular accident, e.g. patients with ischaemic heart or cerebrovascular disease respectively, similar considerations may apply. It is advisable to initiate treatment at lower dosages than those usually recommended for uncomplicated patients where high risk patients are involved.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses. Once the blood pressure has increased further doses can usually be given without the same difficulty. The magnitude of the decrease in blood pressure is greatest early in the course of treatment. This effect stabilises within a week or two, and generally returns to pre-treatment levels, without a decrease in therapeutic efficacy within two months.

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 attention.

Hyperkalaemia

Because the ACE inhibitors decrease the formation of angiotensin II and the subsequent production of aldosterone, serum potassium concentration exceeding 5.5 mEq/L may occur, although frank hyperkalaemia is uncommon. Hyperkalaemia is more likely to occur in the following patients:

- those with some degree of renal impairment
- those treated with potassium-sparing diuretics or potassium supplements
- those consuming potassium-containing salt substitutes or other drugs associated with increases in serum potassium (e.g. heparin).

Diabetics, and elderly diabetics particularly, may be at increased risk of hyperkalaemia.

It is recommended that patients taking an ACE inhibitor should have serum electrolytes (including potassium, sodium, and urea) measured from time to time. This is more important in patients taking diuretics.

Cough

A persistent dry (non-productive) cough has been reported with all of the ACE inhibitors. This cough appears to be a class-effect and occurs in between 2% to 15% depending upon the drug, dosage and duration of use. The cough, which may be due to increased bronchial reactivity, appears to be more common in women (approximately 2:1) and is often worse when lying down. The cough may resolve or diminish with continued use, or with dose reduction, but usually returns on rechallenge. The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins which accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases. No residual effects have been reported. ACE-inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Renal Function

Evaluation of the patient should include assessment of renal function prior to initiation of therapy and at appropriate intervals thereafter (see **DOSAGE AND ADMINISTRATION)**.

Hypertension

There have been increases in serum concentrations of blood urea nitrogen (BUN) and serum creatinine after reduction of blood pressure with captopril. This occurred in some patients with renal disease, particularly those with renal artery stenosis, and developed usually when captopril was administered in conjunction with a diuretic. This may require a dosage reduction of captopril and/or discontinuation of diuretic. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion; therefore titration to acceptable blood pressure may be necessary.

Captopril should be administered cautiously in patients with low renal perfusion (bilateral renal artery stenosis, renal artery stenosis to a solitary kidney). The renin-angiotensin system may be an important regulator of glomerular filtration rate in such patients.

Evaluation of the hypertensive patient should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**). If a deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another. In these patients usage of another class of anti-hypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea nitrogen and serum creatinine.

Heart Failure

Upon long-term treatment with captopril, approximately 20% of patients develop stable elevations of BUN and serum creatinine greater than 20% above normal or baseline. Less than 5% of patients, generally those with severe pre-existing renal disease, required discontinuation of treatment due to progressively increasing creatinine. Subsequent improvement probably depends upon the severity of the underlying renal disease.

Use in Pregnancy (Category D)

As with all ACE inhibitors, captopril should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with captopril and avoided during the treatment.

If the patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment.

If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.

When used in pregnancy, ACE inhibitors can cause injury and even death to the developing foetus.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with foetal and neonatal injury including hypotension, neonatal skull hypoplasia anuria, reversible and irreversible renal failure and death.

Oligohydramnios has been reported, presumably resulting from decreased foetal renal function. Oligohydramnios has been associated with foetal limb contractures, craniofacial deformities, hypoplastic lung development and intra-uterine growth retardation. Prematurity and patent ductus arteriosus have also been reported.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during 1st trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared to no exposure.

Australian Categorisation Definition of Category D :
Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying text above should be consulted for further details.

Use in Lactation

Following oral administration, concentrations of captopril in human breast milk are 1% or less of those in maternal blood. The effect of this low level of captopril on the breast-fed infant has not been determined. Caution should be exercised when captopril is administered to a woman who is breast feeding and in general breast feeding should be interrupted.

Use in Diabetic Nephropathy

In managing a patient with microalbuminuria the physician should be mindful of the importance of reducing other risk factors for progression to proteinuria, for example, the need to maintain adequate control of blood glucose and blood pressure.

The physician should also alert normotensive patients with diabetic nephropathy to the possibility of the rare occurrence of hypotension during treatment with captopril.

Surgery / Anaesthesia

Captopril will block angiotensin II formation secondary to compensatory renin release. This is particularly important in patients undergoing major surgery or during anaesthesia with agents that produce hypotension since the effects of captopril may lead to hypotension, which can be corrected by volume expansion.

Carcinogenicity

Two year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Paediatric Use

Safety and effectiveness in children have not been established although there is limited experience in children with secondary hypertension and varying degrees of renal failure. Dosage, on a weight basis, was comparable to that used in adults. Captopril should only be used if the potential benefit justifies the risk.

Interactions with Other Medicines

Combination Use of ACE Inhibitors or Angiotensin Receptor Antagonists, Anti-Inflammatory Drugs and Thiazide Diuretics

Concomitant use of a rennin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy, and periodically thereafter.

Hypotension – Patients on Diuretic Therapy

When a diuretic is added to the therapy of a patient receiving captopril, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure usually within the first hour after initiation of therapy with captopril. The possibility of hypotensive effects may be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. If it is not possible to discontinue the diuretic, the starting dose of captopril should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until blood pressure has stabilised.

Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Agents Affecting Sympathetic Activity

Agents that affect sympathetic activity (e.g. ganglionic blocking agents or adrenergic neurone blocking agents) should be used with caution in conjuction with captopril. The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril but the overall response is less than additive. Patients will need to be closely supervised.

Agents Increasing Serum Potassium including Potassium Sparing Diuretics

Captopril decreases aldosterone production, therefore elevation of serum potassium may occur. Potassium-sparing diuretics (e.g. spironolactone, triamterene, or amiloride) or potassium supplements should be given only for documented hypokalaemia, and then with caution, since they may lead to a significant increase in serum potassium. Salt substitutes containing potassium should also be used with caution.

Non-Steroidal Anti-Inflammatory Drugs (NSAID)

There is some evidence to suggest that concomitant administration of non-steroidal anti-inflammatory drugs such as indomethacin may reduce the response to ACE inhibitors, but further data are needed to clarify whether such an effect is of clinical significance.

Also, concomitant administration of NSAID and ACE inhibitors may increase the risk of hyperkalaemia.

Agents having Vasodilator Activity

Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available. Therefore, glyceryl trinitrate or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting captopril. If these drugs are resumed during captopril therapy, such agents should be administered cautiously, and perhaps at lower dosage.

Captopril has been reported to act synergistically with peripheral vasodilators such as minoxidil.

Haemodialysis Membranes

Hypersensitivity-like (anaphylactoid) reactions have been reported with high-flux dialysis membranes (see **PRECAUTIONS**).

Allopurinol

There have been reports of neutropenia and/or Stevens-Johnson Syndrome in patients on captopril and allopurinol.

Azathioprine

Azathioprine has been associated with blood dyscrasias in patients with renal failure who were also taking captopril.

Clonidine

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

Cyclophosphamide

Cyclophosphamide has been associated with blood dyscrasias in patients with renal failure who were also taking captopril.

Procainamide

There have been reports of neutropenia and/or Stevens-Johnson Syndrome in patients on captopril and procainamide.

Effects on Laboratory Tests

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

ADVERSE EFFECTS

Reported incidences are based on clinical trials involving approximately 7000 patients treated with captopril.

More Common Reactions

Cardiovascular

Hypotension occurs in approximately 2% of patients (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). Hypotension may be a serious and/or life-threatening reaction.

Dermatological

Rash occurred in 3.8% of patients with normal renal function and 13.1% of patients with evidence of prior renal functional impairment. The rash is usually pruritic and maculopapular, but rarely urticarial, and generally occurs during the first 4 weeks of treatment. It is usually self-limiting and reversible and may respond to antihistamine therapy. In the majority of patients the condition resolves with the continuation of therapy.

The rash was sometimes accompanied by fever and arthralgia, and in 7 to 10% of patients, by eosinophilia and/or positive antinuclear antibody (ANA) titres.

Respiratory

Cough has been reported in 0.5 to 2% of patients in clinical trials of captopril (see **PRECAUTIONS**).

Taste Disturbances (Dysgeusia)

1.6% of patients receiving 150 mg or less daily of captopril developed a diminution or loss of taste perception. At doses in excess of 150 mg per day, 7.3% of patients experienced this effect. Taste impairment is reversible and usually self-limited to 2 to 3 months, and even with continued drug administration. Weight loss may be associated with the loss of taste.

Less Common Reactions

Cardiovascular

Tachycardia, chest pain and palpitations have been observed in about 1% of patients.

Angina pectoris, myocardial infarction, Raynaud's phenomenon and congestive heart failure have occurred in 0.2 to 0.3% of patients. Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances/orthostatic hypotension, syncope have also been reported.

Gastrointestinal

Gastric irritation, abdominal pain, and panreatitis have been reported. Nausea, vomiting, diarrhoea, anorexia and constipation may also occur. Stomatitis, resembling aphthous ulcers, tongue ulceration and a scalded sensation of the oral mucosa have been reported. Cases of hepatitis have been reported in association with captopril administration. The predominant form of captopril-associated hepatic injury is cholestasis although mixed or pure hepatocellular injury has also been reported.

Genitourinary

Proteinuria (see **PRECAUTIONS**).

Renal insufficiency, acute renal failure, polyuria, oliguria and urinary frequency have been reported in 0.1 to 0.2% of patients. Cases of nephrotic syndrome and glomerulopathy have also been reported.

Haematological & Reticuloendothelial

Neutropenia/agranulocytosis (see **PRECAUTIONS**). Neutropenia/agranulocytosis may be serious and/or life-threatening reactions.

Reversible lymphadenopathy, eosinophilia, anaemia, pancytopenia and thrombocytopenia have been reported.

Dermatological

Angioedema involving extremities, face, lips, mucous membranes, tongue, glottis or larynx has been observed in approximately 1 in 1000 patients (see **PRECAUTIONS**). Angioedema may be a serious and/or life-threatening reaction.

Flushing or pallor has been reported in 0.2 to 0.5% of patients. Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis, photosensitivity are other less common dermatological reactions.

Other

Paraesthesias of the hands, serum sickness-like syndrome, myalgia, fatigue, malaise and dizziness have been reported. Dry mouth, dysnoea, bronchospasm, disturbed vision, itching and/or dry eyes, impotence, loss of libido and insomnia have occurred rarely, often in patients on multiple drug therapy. Asthenia and gynecomastia.

Serious of Life Threatening Reactions

Angiodema / Hypotension (see **PRECAUTIONS**).

Neutropenia / Agranulocytosis (see **PRECAUTIONS**).

Altered Laboratory Findings

Elevation of liver transaminases, alkaline phosphatase and serum bilirubin have occurred, but no causal relationship to captopril use has been established.

A transient elevation of BUN and serum creatinine may occur, especially in patients who are volume-depleted or who have renovascular hypertension. In instances of rapid reduction of long-standing or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN.

Small increases in the serum potassium concentration frequently occur especially in patients with renal impairment (see **PRECAUTIONS**). Hyponatraemia may occur, particularly in patients receiving a low sodium diet or concomitant diuretics.

Changes in blood cell counts and anaemia have occurred during treatment with captopril (see **ADVERSE EFFECTS, Haematological & Reticuloendothelial**).

Post-Introduction Safety Experience

Other clinical adverse effects reported since the medicine was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Foetal/ Neonatal Morbidity and Mortality

The use of ACE inhibitors during pregnancy has been associated with foetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased foetal renal function; oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported. More recently, prematurity, patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have been reported following exposure limited to the first trimester of pregnancy. (See **PRECAUTIONS Use in Pregnancy**).

Musculoskeletal

Myasthenia.

Nervous/Psychiatric

Ataxia, confusion, depression, nervousness, somnolence.

Respiratory

Eosinophilic pneumonitis, rhinitis.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

DOSAGE AND ADMINISTRATION

Following administration of captopril, a first dose hypotensive effect, severe in some patients may occur. To minimise this effect, the dosage should be individualised and titrated from a low starting dose to the maintenance dose.

Captopril should be taken one hour before meals.

Hypertension

Initiation of therapy requires consideration of recent anti-hypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. Where possible, the patient's previous anti-hypertensive drug regimen should be discontinued for one week before starting captopril.

A starting dose of 12.5 mg is appropriate in most patients. The dose may then be increased to 25 mg twice a day. If a satisfactory reduction of blood pressure has not been achieved after 2 to 4 weeks, the dose of captopril may be increased to 50 mg twice a day. When captopril therapy is used alone,

concomitant sodium restriction may be beneficial. In patients in whom a satisfactory reduction in blood pressure is not achieved after a further 2 weeks at this dosage, it is likely that the hypertension may have a substantial volume-dependent component. In these patients it may be appropriate to add a thiazide diuretic. The diuretic dose may be increased at 1 to 2 week intervals until its highest usual antihypertensive dose is reached. The usual effective dose of captopril in mild to moderate hypertension does not exceed 50 mg twice a day.

In patients with severe refractory hypertension or on high doses of diuretics, low salt diet or dialysis, a lower starting dose (6.25 to 12.5 mg) may be used, with titration to daily doses of 25 mg or 50 mg twice a day.

Initiation of captopril therapy requires close medical supervision if captopril is being started in a patient already receiving a diuretic (see **PRECAUTIONS**, Interactions with Other Medicines).

In severe hypertension where further blood pressure reduction is required, larger or more frequent dosing may be necessary. A daily dose of 75 mg twice a day of captopril should not normally be exceeded.

For patients with accelerated or malignant hypertension, particularly those unresponsive to conventional therapy, it may be necessary to implement the schedule given above at intervals of 24 hours, under continuous medical supervision, until a satisfactory blood pressure response is obtained or the maximum dose of captopril is reached.

Myocardial Infarction

Therapy may be initiated as early as 3 days following a myocardial infarction. After an initial dose of 6.25 mg, captopril therapy should be increased as tolerated to 25 mg three times daily during the next several days and to a final target dose of 50 mg three times daily over the next several weeks.

If symptomatic hypotension occurs, a dosage reduction may be required. Subsequent attempts at achieving the target dose of 150 mg should be based on the patient's tolerance to captopril.

Captopril may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, aspirin and beta-blockers.

Heart Failure

Captopril therapy must be started under close medical supervision. It should be added to conventional treatment with a diuretic (and digitalis where indicated).

Patients with cardiac failure may demonstrate sensitivity to the effects of captopril in the early stages of therapy.

In patients in whom greater sensitivity may be suspected (e.g. sodium depletion and/or high doses of diuretics), the hypotensive effects of the first dose may be minimised by the use of 2.5 mg starting dose. This product should not be used to initiate therapy in such patients as the smallest achievable dose with Terry White Chemists Captopril tablets is 6.25 mg. In other patients, a starting dose of 6.25 mg three times a day may be used, although a transient hypotensive effect may occur at this dosage.

The maintenance dosage of captopril is usually in the range 25 mg to 75 mg twice daily. Where possible, a period of at least 2 weeks should be allowed before dose increase within this range. A maximum daily dose of 150 mg should normally not be exceeded.

Patients treated for severe congestive heart failure should be cautioned to increase their physical activity slowly.

Diabetic Nephropathy

The recommended dose of captopril in patients with diabetic nephropathy is 75 to 100 mg daily, in divided doses.

Clinical trials in normotensive type 1 diabetic patients with microalbuminuria (albumin excretion rate between 30–300 mg/day) showed that captopril at a dose of 50 mg twice daily attenuated the progression of the disease.

Clinical trials in normotensive and controlled hypertensive type 1 diabetic patients with overt proteinuria (total protein excretion > 500 mg/day) demonstrated that captorpil at a dose of 25 mg three times daily had significant beneficial effects by reducing the need for dialysis and transplantation or the occurrence of death.

The effects of captopril were independant of, and additional to, its antihypertensive activity.

If further blood pressure reduction is required, other antihypertensive agents such as diuretics, beta-adrenoceptor blockers, centrally acting agents or vasodilators may be used in conjunction with captopril

Patients with Renal Impairment

Captopril excretion is reduced in the presence of impaired renal function. Accordingly, for patients with significant renal impairment, initial daily dosage of captopril should be reduced, and smaller increments utilised for titration, which should be quite slow (1 to 2 week intervals). After the desired therapeutic effect has been achieved, the total daily dose should be reduced or the dose intervals increased.

Captopril is removed by haemodialysis.

When concomitant diuretic therapy is required in patients with impaired renal function, a loop diuretic (e.g. frusemide) rather than a thiazide diuretic is preferred.

OVERDOSAGE

Treatment should be symptomatic if overdosage occurs.

Correction of hypotension would be of primary concern. For restoration of blood pressure, volume expansion with an intravenous infusion of normal saline is the treatment of choice.

Although captopril may be removed from the adult circulation by haemodialysis, there is inadequate data concerning the effectiveness of haemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril. There is no information concerning exchange transfusion for removing captopril from the general circulation.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Terry White Chemists Captopril 12.5 mg tablets in packs of 90; white, capsule-shaped, flat-faced, bevelled-edge tablets, partially bisected on both sides; one side engraved “12.5”, other side engraved “APO”. AUST R 73398.

Terry White Chemists Captopril 25 mg tablets in packs of 90; white, square, biconvex; one side engraved “APO” over “25”, other side quadrisected. AUST R 74003.

Terry White Chemists Captopril 50 mg tablets in packs of 90; white, oval, biconvex; partially bisected and engraved “APO-50”, other side plain. AUST R 74007.

The excipients in Terry White Chemists Captopril tablets are: lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica.

Store below 30°C. Protect from moisture.

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Terry White Chemists is a registered trade mark of Symbion Pharmacy Services Pty Ltd.

POISONS SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

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