Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Actopril Tablets 12.5mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains captopril 25 mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round, flat, uncoated tablets, scored on both sides, 8mm in diameter.

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.

4.2 Posology and method of adminstration

For oral administration only.

Captopril is best taken about an hour before meals and should be taken at the same times each day to improve compliance.

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

Initiation of therapy requires, if possible, correction of salt and/or body fluids deficiencies, discontinuation of existing diuretic therapy for two or three days before ACE inhibitors are introduced, and use of the lowest starting dose. If this is not possible, the initial dose should be half of the recommended starting dose.

In patients with malignant hypertension, or severe cardiac insufficiency, initiation of therapy and dose adjustment should be performed in a hospital.

Mild to moderate hypertension: The starting dose is 12.5mg twice daily or 25mg daily. The usual maintenance dose is 25mg twice daily, which can be increased incrementally every 14 to 28 days until a suitable 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 or 25mg 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.

Elderly: The dose should be titrated against 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 to100mg/day was well tolerated in patients with diabetic nephropathy and mild to moderate renal impairment (creatinine clearance at least 30ml/min/l .73m^2). 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/1.73m^2), 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.

History of angioneurotic oedema associated with previous use of ACE inhibitors.

Hereditary or idiopathic angioneurotic oedema.

Use during Pregnancy and Lactation.

4.4 Special warnings and special precautions for use

Precautions: Patients should be assessed for renal function prior to the start of therapy and at appropriate intervals during therapy. Captopril should not be used in patients with aortic stenosis or outflow tract obstruction.
As limited experience has been obtained in the treatment of acute hypertensive crises, the use of captopril should be avoided in these patients.

Warnings: Any adverse reactions to captopril are usually associated with impaired renal function since the drug is mainly excreted by the kidneys. The dose used should not exceed the amount needed for adequate control and should be reduced in renal impairment.

Hypotension: A profound drop in blood pressure may occur, particularly after the initial dose. In uncomplicated hypertensive patients, symptomatic hypotension rarely occurs. Occurrence is more likely in patients who have been volume depleted due to treatment with a diuretic, dietary salt restriction, dialysis, diarrhoea or vomiting. Reports have mainly been for patients with severe heart failure with or without associated renal insufficiency.

Patients on high doses of loop diuretics, or with hyponatraemia or functional renal impairment, are more likely to experience this effect. Treatment of such patients should begin under close medical supervision, (within a hospital preferred), using low doses and careful dose titration. Use of diuretics should be stopped temporarily if possible. These considerations are also applicable to patients with angina pectoris or cardiovascular disease, (excessive hypotension could cause myocardial infarction or cerebrovascular accident).

In the event of hypotension, the patient should be placed in a supine position.
Volume repletion may be required (intravenous normal saline), if hypotension occurs after the first dose, subsequent careful dose titration with captopril is not precluded after effective management.

Patients with renovascular hypertension: Patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or unilateral renal artery stenosis given captopril are at an increased risk of severe hypotension and renal insufficiency. Even in patients with unilateral renal artery stenosis, renal function loss may be associated with mild changes in serum creatinine.

Treatment should be initiated in hospital under close medical supervision, using low doses and careful dose titration. During the first weeks of treatment, use of diuretics should be discontinued and renal function should be monitored.

Patients with renal insufficiency: Patients with renal insufficiency may require reduced or less frequent doses (inhibition of the renin-angiotensin-aldosterone system may alter renal function in susceptible individuals) and should be treated with caution. Renal function should be monitored closely, as appropriate, during treatment. Reports of renal failure associated with captopril have occurred mainly in patients with severe heart failure or underlying renal disease (e.g. renal artery stenosis). Increases in blood urea and creatinine concentrations have occurred in some patients with apparently no pre-existing renal disease when a diuretic is used concurrently.

Reduction of the dose of captopril and/or discontinuation of the diuretic may be necessary. Renal function should be monitored during the first weeks of treatment. Patients treated with captopril who are dialysed with high-flux polyacrylonitrile membranes are likely to suffer anaphylactoid reactions (e.g. facial swelling, flushing, hypotension and dyspnoea) within a few minutes after dialysis has begun. Use of an alternative membrane or an alternative antihypertensive drug is recommended.

Angioedema: Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx may occur particularly during the first weeks of treatment with ACE inhibitors. If a severe case of angioedema develops after long-term treatment with an ACE inhibitor (occurs rarely), treatment should be stopped promptly and a product from another class of drugs used instead.

Angioedema involving the tongue, glottis or larynx may be fatal, and emergency treatment, including the following, should be provided; an immediate subcutaneous injection of 0.3-0.5ml adrenaline solution 1 : 1000 or slow intravenous adrenaline l mg/ml (dilution instructions to be observed), electrocardiogram or blood pressure control, hospitalisation and observation for a minimum of 12 to 24 hours. Hospitalisation should be maintained until all symptoms have disappeared.

Cough: Captopril treatment may be associated with a dry non-productive cough which disappears when treatment is stopped (see section 4.8).

Hyperkalaemia: This may occur during the treatment, particularly if renal insufficiency and/or heart failure are present. Use of potassium supplements or potassium-sparing diuretics may result in significant increases in plasma potassium and are not recommended. Serum potassium should be monitored frequently if such products are used concomitantly.

Surgery/anaesthesia: Hypotension or a hypotensive shock may occur in patients undergoing major surgery or during

anaesthesia due to enhancement of other hypotensive potentials. Adequate volume management should be provided if discontinuation of captopril is impossible.

Aortic stenosis/Hypertrophic cardiomyopathy: Use with caution in patients with obstruction of the outflow tract of the left ventricle.

Elderly/Children: See section 4.2.

Neutropenia/Agranulocytosis: The risk of neutropenia appears to be related to dose and product type dependent and the patient's clinical status. The condition, which is reversible, is rare in uncomplicated patients, but may occur in patients with renal impairment especially if associated with collagen vascular disease (e.g. systemic lupus erythematosus, scleroderma) and treatment with immunosuppressives.

Proteinuria: It may occur if renal function impairment pre-exists or relatively high doses are used.

4.5 Interaction with other medicinal products and other forms of interaction

Not Recommended

Potassium sparing diuretics or potassium supplements: Use with potassium sparing diuretics or potassium supplements is not recommended (diuretic-induced potassium loss is reduced by captopril). Significant increase in serum potassium may result from concurrent use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or potassium containing salt substitutes. If hypokalaemia necessitates their use, they should be used with caution and serum potassium monitored frequently.

Precaution for use

Diuretics: After captopril treatment has started, excessive reduction in blood pressure may occur in patients receiving diuretics and particularly those who are volume- and/or salt-depleted. Risk of hypotensive effects may be reduced by; stopping diuretic treatment, increasing volume or salt intake before administration of captopril, starting treatment with lower doses of captopril and, if necessary, increasing dosage with caution.

Lithium: Excretion of lithium may be reduced if lithium and captopril are administered concomitantly. Frequent monitoring of serum lithium levels should be performed.

Anaesthetic drugs: The effect of anaesthetic agents may be enhanced.

Narcotic drugs/Antipsychotics: Postural hypotension may occur.

Antihypertensive agents: Increase the hypotensive effect of captopril.

Allopurinol, cytostatic or immunosuppressive agents, corticosteroids or procainamide: The risk of leucopenia may be increased if used concomitantly with captopril.

Take into account

*Non-steroidal anti-inflammatory drugs:*the antihypertensive effect of captopril may be reduced by administration of a NSAID. An additive effect on serum potassium increase has been described when NSAIDs and captopril are used concomitantly, while renal function may be reduced. Such effects, which occur particularly in patients with compromised renal function, are in principle reversible.

Antacids: Cause reduced bio-availability of captopril.

Sympathomimetics: The antihypertensive effects of captopril may be reduced. Patients should be carefully monitored.

Alcohol: The hypotensive effect of captopril is increased.

Food: The bio-availability of captopril may be decreased.

Concomitant administration of ACE-inhibitors and anti-diabetic medicines (insulin, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with a risk of hypoglycaemia. This phenomenon may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

4.6 Pregnancy and lactation

No appropriate and well controlled studies have been performed in humans. Foetal and neonatal morbidity and mortality may occur when ACE inhibitors (these can cross the placenta) are administered to pregnant women.

Neonatal hypotension, renal failure, face or skull deformities and/or death have been associated with exposure of the foetus during the second and third trimesters. Maternal oligohydramnios (indicative of decreasing foetal renal function) has been reported. Reports of limb contractures, craniofacial deformities, hypoplastic lung development and intra-uterine growth retardation have been associated with oligohydramnios. Close observation of infants exposed in utero for hypotension, oliguria and hyperkalaemia should be carried out. If oliguria occurs, treatment consists of support of blood pressure and renal perfusion.

Intra-uterine growth retardation, prematurity, patent ductus arteriosus and foetal death have been reported, but their relationship to the ACE inhibition or the underlying maternal disease is unknown.

The effect of exposure of the foetus during the first trimester only is unknown. If pregnancy occurs during treatment, the pregnant woman should be informed of the possible hazard to the foetus.

Use of ACE inhibitors during breast feeding by lactating mothers is not recommended (ACE inhibitors may be excreted into breast milk and their effects on the nursing infant are unknown).

4.7 Effects on ability to drive and use machines

No studies on the effect of the ability to drive have been performed. The possibility of the occurrence of occasional dizziness or weariness should be taken into account when driving or operating machinery.

4.8 Undesirable effects

Observed side effects with treatment with Captopril:

Cardiovascular: Severe Hypotension has been observed after the start of treatment or when the dose has been increased, especially in high risk patients (see section 4.4). Dizziness, feeling weak, impaired vision with, in rare cases, disturbance of consciousness (syncope) may occur.
Individual incidents of the following have been reported in association with hypotension; tachycardia, palpitations, arrhythmias, angina pectoris, myocardial infarction, transient ischaemic attacks and cerebral haemorrhage.

Renal: Intensification of renal insufficiency may occur. Acute renal failure has been reported (see section 4.4).

Respiratory: Induction of cough in a large number of patients has been reported. Rare reports have been made of dyspnoea, sinusitis, rhinitis, glossitis, bronchitis and bronchospasm. Fatal airway obstruction has occurred in angioneurotic oedema involving the upper airways.

Gastro-intestinal: Nausea, vomiting, abdominal pain, indigestion, diarrhoea, constipation and dry mouth can occur occasionally. Rarely cholestatic icterus, hepatitis, pancreatitis and ileus have been associated with ACE inhibitor therapy.

Skin: Allergic and hypersensitivity reactions (e.g. rash, pruritus, urticaria, erythema multiforme, Stevens-Johnson's syndrome, toxic epidermic necrolysis, psoriasis-like efflorescence, alopecia) are rare and may be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA (anti-nuclear antibody) -titres. The onset of

angioneurotic oedema involving the face and oropharyngeal tissues has been reported (see section 4.4).

Nervous System: Headaches, dizziness, weariness occur occasionally. Depression, sleep disorders, paraesthesias, impotence, balance disorders, confusion, tinnitus, blurred vision and taste disturbances are rare.

Drug/Laboratory parameters: Reversible (on stopping treatment) increases in blood urea and plasma creatinine may result, particularly if renal insufficiency, severe heart failure or renovascular hypertension is present.

Decreases in haemoglobin, haemocrit, platelets and white cell count, and individual incidents of agranulocytosis or pancytopenia, in addition to elevated liver enzymes and serum bilirubin, have been reported in a few patients. Haemolytic anaemia has been reported in some patients with a congenital deficiency of glucose-6-phosphate dehydrogenase.

4.9 Overdose

Overdosage symptoms comprise severe hypotension, shock, stupor, bradycardia, electrolyte disturbance and renal failure.
In cases of overdosage patients should be kept under close supervision, (intensive care unit preferred). Frequent monitoring of serum electrolytes and creatinine should be performed.

Treatment will depend on the nature and severity. If ingestion is recent, measures should be taken to prevent absorption and speed elimination (e.g. gastric lavage and administration of absorbents and sodium sulphate within 30 minutes of drug intake). In cases of hypotension, the patient should be placed in the shock position and salt and volume supplementation administered rapidly.

Consideration should be given to the administration of angiotensin II. Atropine should be used to treat bradycardia or extensive vagal reactions. Use of a pacemaker can be considered. Dialysis may be used to remove captopril from the circulation but high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The benefits of ACE inhibitors in the treatment of hypertension and in heart failure seem to result mainly from the suppression of the plasma renin-angiotensin-aldosterone system. Renin, an endogenous enzyme produced by the kidneys, is released in to the circulation and converts angiotensinogen to angiotensin I, (a relatively inactive decapeptide). Angiotensin Converting Enzyme, (a peptidyldipeptidase) converts angiotensin I to angiotensin II, a potent vasoconstrictor, which causes arterial vasoconstriction and increased blood pressure. It also stimulates the adrenal gland to secrete aldosterone. Decreased plasma angiotensin II results from ACE inhibition.

This leads to reduced vasopressor activity and aldosterone secretion, the latter reduction is small but may result in small increases in serum potassium concentrations together with loss of sodium and fluid. An increase in plasma renin activity occurs when the negative feedback of angiotensin II on renin secretion stops.

The converting enzyme also degrades the kinin peptide bradykinin (a potent vasodepressive) to inactive metabolites. Consequently ACE inhibition causes increased activity of the circulating and local kallikrein-kinin system, which contributes to peripheral vasodilation (prostaglandin system activated). This mechanism, which is responsible for certain side-effects, may be involved in the hypotensive effect of captopril.

Administration of captopril to patients with hypertension reduces supine and standing blood pressure to about the same extent without a compensating increase in heart rate. Peripheral arterial resistance is reduced with either no change or an increase in cardiac output. There is an increase in renal blood flow and glomerular filtration rate is usually unchanged.

Optimal blood pressure reduction may take several weeks to obtain.
Maintenance of antihypertensive effects occurs during long term treatment.

Rapid increase in blood pressure has not been associated with abrupt cessation of treatment.

Treatment is effective even in patients with low-renin hypertension.
Antihypertensive effects have been studied in different races, but monotherapy produced a smaller average response in black hypertensive patients (generally a low-renin population) than in non-black patients. There is no difference if a diuretic is used.

In patients with heart failure, the haemodynamic effects are due to both arteriolar and venodilation. A reduction in systemic vascular resistance and an increase in venous capacity occurs, there by decreasing pre- and after-load. This results in; decrease in left ventricular filling pressure pulmonary capillary wedge pressure, increased cardiac output, unchanged or decreased heart rate. Improvement of the clinical signs and symptoms of heart failure and increased exercise capacity will occur. During long-term treatment, these effects are maintained.

5.2 Pharmacokinetic properties

Captopril is rapidly absorbed as an oral dose, with a bioavailability of about 70% after fasting, this is decreased by 30-40% if the drug is taken with food. It is metabolised chiefly to the disulfide with less than half the oral dose excreted unchanged in the urine.

Captopril is distributed to most body tissues with the notable exception of the central nervous system. Although the half-life is not clearly established most captopril is eliminated from the body within six hours.

Captopril is administered two or three times a day about one or two hours before meals. Maximal blood pressure response is seen about two to four hours after the oral dose. 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.

5.3 Preclinical safety data

Chronic oral toxicity studies carried out in animals show drug related toxicity including haematopoiesis, renal toxicity, ulceration of the stomach and changes in the retinal blood vessels.

At levels in excess of therapeutic doses, the following conditions were observed: anaemia, leucopenia, thrombocytopenia and bone marrow suppression. Captopril has been shown to cause hyperplasia of the juxtaglomerular apparatus of the kidneys at doses 7 to 200 times the maximum recommended human dose.

Rabbit studies showed gastrointestinal ulceration at 30 times maximum dose after a period of only 5 to 7 days. In a two year study in rats, irreversible changes in the retinal blood vessels in a dose related pattern appeared in the second year of the study.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinised maize starch
Microcrystalline cellulose
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

AL/PVC blister packs.
Pack sizes: 10, 56 and 100

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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D-61118 Bad Vilbel
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8 MARKETING AUTHORISATION NUMBER

PA 593/11/2

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