NEW ZEALAND DATA SHEET

1 PRODUCT NAME

CAPOTEN Captopril Oral Solution 5mg/mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CAPOTEN oral solution comes in one strength and contains 5 mg of captopril per mL of solution.

Excipients with known effect: sodium benzoate

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

CAPOTEN Oral solution contains captopril 5 mg/mL, clear, colourless, unsweetened, flavour free.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension: CAPOTEN (captopril) is indicated for the treatment of hypertension.

In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis (see section 4.4 Special warnings and precautions for use).

CAPOTEN 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: CAPOTEN 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 hospitalisations for congestive heart failure in these patients. The efficacy data for the use of CAPOTEN following myocardial infarction are strongest for initiation of therapy beyond 3 days post-infarct.

Heart Failure: CAPOTEN (captopril) is indicated for the treatment of heart failure. In symptomatic patients it is recommended that CAPOTEN be administered together with a diuretic.

Diabetic Nephropathy: CAPOTEN is indicated for the treatment of diabetic nephropathy in patients with Type 1 insulin-dependent diabetes mellitus.

4.2 DOSE AND METHOD OF ADMINISTRATION

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.

CAPOTEN (captopril) should be taken one hour before meals.

Hypertension

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. If possible, discontinue the patient's previous antihypertensive drug regimen for one week before starting CAPOTEN.

In most patients, a starting dose of 12.5mg may be used. The dose may than be increased to 25 mg twice daily. If a satisfactory reduction of blood pressure has not been achieved after 2-4 weeks, the dose of CAPOTEN (captopril) may be increased to 50 mg twice daily. Concomitant sodium restriction may be beneficial when CAPOTEN is used alone.

In patients in whom a satisfactory reduction in blood pressure is not achieved after a further two 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 one to two week intervals until its highest usual antihypertensive dose is reached.

The usual effective dose of CAPOTEN in mild to moderate hypertension does not exceed 50mg twice daily.

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

If CAPOTEN is being started in a patient already receiving a diuretic, CAPOTEN therapy should be initiated under close medical supervision (see section 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

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 daily. CAPOTEN 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 CAPOTEN (captopril) is reached.

Myocardial Infarction

Therapy may be initiated as early as 3 days following a myocardial infarction. After an initial dose of 6.25mg, CAPOTEN therapy should be increased as tolerated to 25mg three times daily during the next several days and to a final target dose of 50mg 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 150mg should be based on the patient's tolerance to CAPOTEN.

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

Heart Failure

CAPOTEN (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 CAPOTEN in the early stages of therapy.

In patients in whom greater sensitivity may be suspected (eg: 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. In other patients, a starting dose of 6.25 mg three times daily may be used, although a transient hypotensive effect may occur at this dosage.

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

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

Diabetic Nephropathy:

In patients with diabetic nephropathy, the recommended dose of Capoten is 75 to 100 mg daily, in divided doses.

Clinical trials in normotensive type 1 diabetic patients with microalbuminuria (albumin excretion rate between 30 - 300mg/day) showed that Capoten at a dose of 50mg 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 >500mg/day) demonstrated that Capoten 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 Capoten 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 Capoten.

Patients with Renal Impairment

CAPOTEN excretion is reduced in the presence of impaired renal function.

Accordingly, for patients with significant renal impairment, initial daily dosage of CAPOTEN should be reduced, and smaller increments utilized for titration, which should be quite slow (one to two week intervals). After the desired therapeutic effect has been achieved, the total daily dose should be reduced, or the dose intervals increased.

CAPOTEN is removed by haemodialysis.

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

4.3 CONTRAINDICATIONS

A history of previous hypersensitivity to Capoten (captopril or the inactive ingredients).

Pregnancy (see section 4.6 **Use in Pregnancy**).

Patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an angiotensin converting enzyme inhibitor.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Anaphylactoid and Possibly Related Reactions

Possibly because angiotensin-converting enzyme is essential for degradation of endogenous bradykinin, patients receiving ACE inhibitors are subject to a variety of adverse reactions producing effects ranging from relatively mild, such as cough (see section 4.4 Special warnings and precautions for use), to serious such as the following:

Head and neck angioedema

Severe life-threatening angioedema has been reported rarely with most of the angiotensin converting enzyme (ACE) inhibitors. The overall incidence is approximately 0.1% to 0.2%. There seems to be no sex difference in the incidence of angiodema 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. The aetiology is thought to be nonimmunogenic 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 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 adrenalin 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 is 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.

Intestinal angioedema

Intestinal angioedema has been reported rarely in patients treated with ACEinhibitors. 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 the 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 desensitisations procedures.

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

Patients hemodialysed with 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 apheresis with dextran sulfate absorption. These combinations should therefore be avoided, either by use of a different class of medication or alternative membranes (eg. cuprophane or polysulphone PSF for haemodialysis).

Proteinuria

Total urinary proteins greater than 1g per day were seen in about 0.7% of patients receiving CAPOTEN, the majority of whom had prior renal disease, or were receiving relatively high doses (in excess of 150 mg per day), or both. In mild to moderate hypertensive patients the incidence

dropped to 0.06%. Alterations 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 CAPOTEN was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Although membranous glomerulopathy was found in biopsies taken from proteinuric patients, a causal relationship to CAPOTEN has not been established since pretreatment biopsies were not taken and membranous glomerulopathy has been shown to occur in hypertensive patients not receiving CAPOTEN.

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 of 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 CAPOTEN, but 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.

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

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

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

Neutropenia was noted 2 to 13 weeks after CAPOTEN therapy had been started and it developed relatively slowly, the white 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 per cent 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 and the effect was no longer apparent after twelve weeks in most patients. The significance of these changes in uncertain.

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

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

In general, neutrophils returned to normal in about two weeks after CAPOTEN was discontinued, and serious infections were limited to clinically complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or 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 CAPOTEN is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately two week intervals for about three months, then periodically.

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

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 section 4.4 Special warnings and precautions for use, section 4.5 Interactions with other medicines and other forms of interactions and section 4.8 Undesirable effects).

In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure greater than 20% are recorded in about half of the patients. This transient

hypotension may occur after any of the first several doses and is usually well tolerated, producing either no symptoms or brief mild lightheadedness, 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 CAPOTEN. 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.

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive azotemia, 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 12.5mg twice daily or three times daily) 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.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident, respectively. In all high risk patients, it is advisable to initiate treatment at lower dosages than those usually recommended for uncomplicated patients.

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 which usually can be given without difficulty once the blood pressure has increased. The magnitude of the decrease is greatest early in the course of treatment; this effect stabilizes within a week or two, and generally returns to pre-treatment levels, without a decrease in therapeutic efficacy, within two months.

Hyperkalaemia

Because the ACE inhibitors decrease the formation of angiotensin II and the subsequent production of aldosterone, serum potassium concentrations exceeding 5.5 mEq/L may occur, although frank hyperkalaemia is uncommon. Hyperkalaemia is more likely in patients with some degree of renal impairment, those treated with potassium-sparing diuretics or potassium supplements, and in those consuming potassium-containing salt substitutes or other drugs associated with increases in serum potassium (eg: 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 ACEinhibitors and appears to be a class-effect. In studies, with various ACE inhibitors, the incidence of cough varies 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 often worse when lying down. It 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.

Heart Failure: About 20% of patients develop stable elevations of BUN and serum creatinine greater than 20% above normal or baseline upon long-term treatment with captopril. 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.

Dual blockade of the renin-angiotensin-aldosterone system

As a consequence of inhibiting the renin-angiotensin aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the reninangiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

Surgery/Anaesthesia

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

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 CAPOTEN.

Use in hepatic impairment

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.

Use in renal impairment

Hypertension: Some patients with renal disease, particularly those with renal artery stenosis, have developed increases in serum concentrations of blood urea nitrogen (BUN) and serum creatinine after reduction of blood pressure with CAPOTEN (captopril), usually in conjunction with a diuretic. CAPOTEN (captopril) dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion; therefore titration to acceptable blood pressure may be necessary.

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

Evaluation of the hypertensive patients should always include assessment of renal function (see 4.2 Dose and method of Administration). If a deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive 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.

Use in the elderly

No data available

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. CAPOTEN should be used only if the potential benefit justifies the risk.

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Hypotension - Patients on diuretic therapy

When a diuretic is added to the therapy of a patient receiving CAPOTEN, 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 CAPOTEN. 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 CAPOTEN 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.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including COX-2 inhibitor) and a thiazide diuretic may increase 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.

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 coadministered 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
The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving CAPOTEN alone or with diuretics. Therefore, agents affecting sympathetic activity (eg: ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta adrenergic blocking drugs add some further antihypertensive effect to CAPOTEN, but the overall response is less than additive, patients will need to be closely supervised.

Agents increasing serum potassium
Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics (eg: 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 of serum potassium. Salt substitutes containing potassium should also be used with caution.

Non-steroidal anti-inflammatory drugs
There is some evidence to suggest that concomitant administration of nonsteroidal 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. Further, concomitant administration of the two classes of agents may increase the risk of hyperkalaemia.

Agents having vasodilator activity
Data on the effect of concomitant use of other vasodilators in patients receiving CAPOTEN 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 CAPOTEN. If resumed during CAPOTEN therapy, such agents should be administered cautiously, and perhaps at lower dosage.

Haemodialysis membranes
Hypersensitivity-like (anaphylactoid) reactions have been reported with high-flux dialysis membranes (see section 4.4 Special warnings and precautions for use).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No Data Available

Use in pregnancy – Pregnancy Category D

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

If a 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 also been reported, presumably resulting from decreased foetal renal function; oligohydramnios has been associated with foetal limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine 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.

Use in lactation.

Following oral administration, concentrations of CAPOTEN in human breast milk are one per cent or less of those in maternal blood. The effect of this low level of CAPOTEN on the breastfed 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 UNDESIRABLE EFFECTS

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

More Common Reactions

Cardiovascular

Hypotension occurs in about 2% of patients (see section 4.4 Special warnings and precautions for use and section 4.2 Dose and method of administartion).

Dermatological

Rash occurred in 3.8 per cent of patients with normal renal function and 13.1 per cent 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-limited 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 7-10 per cent of patients, by eosinophilia and/or positive antinuclear antibody (ANA) titres.

Cough

Cough has been reported in 0.5-2% of patients in clinical trials of CAPOTEN (see section 4.4 Special warnings and precautions for use).

Taste Disturbances (Dysgeusia)

1.6 per cent of patients receiving 150 mg or less or CAPOTEN (captopril) per day developed a diminution or loss of taste perception. At doses in excess of 150 mg per day, 7.3 per cent of patients experienced this effect. Taste impairment is reversible and usually self-limited to 2-3 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 per cent of patients.

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

Gastrointestinal

Gastric irritation, abdominal pain, and pancreatitis have been reported. Nausea, vomiting, diarrhoea, anorexia and constipation may 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 section 4.4 Special warnings and precautions for use).

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

Haematological and reticuloendothelial

Neutropenia/agranulocytosis (see section 4.4 Special warnings and precautions for use). 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 section 4.4 Special warnings and precautions for use). Flushing or pallor has been reported in 0.2 - 0.5% or patients. Bullous pemphigus, erythema multiforme (including Stevens-Johnson Syndrome), exfoliative dermatitis, photosensitivity.

Other

Paraesthesiae of the hands, serum sickness-like syndrome, myalgia, fatigue, malaise and dizziness have been reported. Dry mouth, dyspnoea, 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 or Life-Threatening Reactions
Angioedema/Hypotension. (see section 4.4 Special warnings and precautions for use)

Neutropenia/Agranulocytosis (see section 4.4 Special warnings and precautions for use).

Altered Laboratory Findings

Elevations 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 longstanding 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 section 4.4 Special warnings and precautions for use). 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 section Undesirable effects -"Haematological and reticuloendothelial" above).

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 section 4.4 Special warnings and precautions for use and section 4.6 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Treatment should be symptomatic if it occurs.

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

While CAPOTEN 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 CAPOTEN; there is no information concerning exchange transfusion for removing CAPOTEN from the general circulation.

For advice on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Administration of CAPOTEN 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 CAPOTEN. 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 volumedepleted patients. No sudden increase in blood pressure after withdrawal of the drug has been observed.

Studies have demonstrated an increase in renal blood flow after administration of CAPOTEN. 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.

Mechanism of action

The mechanism of action of CAPOTEN (captopril) has not yet been fully elucidated; however 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 synthesized 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 angiotensinconverting 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.

CAPOTEN prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxyhydrolase. This is reflected by a decrease in the pressor substance, angiotensin II, and increase in plasma renin activity (PRA). The latter 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.

ACE is identical to "bradykininase" and CAPOTEN (captopril) may also interfere with the degradation of bradykinin. Increased concentrations of bradykinin or prostaglandin E_2 may also have a role in the therapeutic effect of CAPOTEN.

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 randomized, double-blind, placebo-

controlled, multi-centre trial - patients (age 2179 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); hospitalization for heart failure (risk reduction = 20%, p=0.034); clinical recurrent MI (risk reduction = 25%,p=0.011); and coronary revascularization 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 CAPOTEN demonstrate increases in exercise time, ability to perform at higher workloads, and improvement in functional capabilities by 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 it 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, age 18-49 of either gender, with or without hypertension, with type 1 (juvenile type, onset before age 30) insulin-dependent diabetes mellitus, retinopathy, proteinuria ≥500mg per day and serum creatinine ≤ 2.5 mg/dL, were randomized to placebo or CAPOTEN (25 mg three times daily) and followed for up to 4.8 years (median 3 years). To achieve blood pressure control, additional antihypertensive agents (diuretics, beta blockers, centerally active agents or vasodilators) were added as needed for patients in both groups.

The CAPOTEN group had a 51% risk reduction in doubling of serum creatinine (p≤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≤0.01). CAPOTEN treatment resulted in a 30% reduction in urine protein excretion within the first 3 months (p<0.05), which was maintained throughout the trial.The

CAPOTEN group had somewhat better blood pressure control than the placebo group , but 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. CAPOTEN was well tolerated in this patient population.

In two multicentre, double-blind, placebo controlled studies, a total of 235 normotensive patients with insulin-dependent diabetes mellitus of 4-30 years duration with onset before the age of 39 years, retinopathy, serum creatinine within the normal range and microalbuminuria (albumin excretion rate 20200µg/min) were randomized to placebo or CAPOTEN (50mg twice daily) and followed for up to 2 years. CAPOTEN delayed the progression to overt nephropathy (albumin excretion rate >200µg/min i.e. proteinuria ≥ 500mg/day) in both studies (risk reduction 67% to 76%: $p< 0.05$). However, the long term clinical benefit of reducing the progression from microalbuminuria to proteinuria has not been established.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of CAPOTEN, rapid absorption occurs with peak blood levels of approximately 1 µg/mL being found $^1/_2$ to 1 hour after a 100 mg dose. The average minimal absorption is approximately 75 per cent. The presence of food in the gastrointestinal tract reduces absorption by 25 to 40 per cent. 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

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

Approximately 30 per cent of the drug is bound to plasma proteins.

Metabolism

Captopril is extensively metabolized. 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

Captopril and its metabolites (captopril dimer and conjugates with endogenous thiol compounds eg: captopril-cysteine) are excreted principally in the urine. In vitro studies suggest that the metabolites are labile and that interconversions may occur in vivo. Approximately 40 per cent of an administered dose is excreted unchanged in the urine in 24 hours and 35 per cent as metabolites. Total body clearance is approximately 0.8 L/kg/h.

The elimination half-life of CAPOTEN is 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 section 4.2 Dose and methos of administration)

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Inactive ingredients: citric acid, sodium citrate, disodium edetate, sodium benzoate and water (pH adjusted with sodium hydroxide and hydrochloric acid).

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

18 months from date of manufacture

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store Capoten oral solution in a refrigerator at 2 to 8°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Oral solution contains 5mg/mL in 95mL bottles.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any solution remaining 28 days after the bottle is opened should be discarded.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd trading as Healthcare Logistics

58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

Tel: +64 9 918 5100

9 DATE OF FIRST APPROVAL

18 January 2013

10 DATE OF REVISION OF THE TEXT

13 May 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted