SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

BIO CAPTOPRIL 12,5 mg, tablets

BIO CAPTOPRIL 25 mg, tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BIO CAPTOPRIL 12,5 mg: Each tablet contains 12,5 mg captopril.

BIO CAPTOPRIL 25 mg: Each tablet contains 25 mg captopril.

Contains sugar (lactose anhydrous):

BIO CAPTOPRIL 12,5 mg contains 26 mg lactose anhydrous per tablet.

BIO CAPTOPRIL 25 mg contains 52 mg lactose anhydrous per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

BIO CAPTOPRIL 12,5 mg: A white to off-white, round, flat, bevelled edged tablet with a break line debossed on one side and plain on the other side.

BIO CAPTOPRIL 25 mg: A white to off-white, round, flat, bevelled edged tablet with a break line debossed on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BIO CAPTOPRIL is indicated for the treatment of mild to moderate hypertension in adult patients.

It may be used alone or in combination with other antihypertensive medicines, especially thiazide-type diuretics. The blood pressure lowering effects of BIO CAPTOPRIL and thiazides are additive.

BIO CAPTOPRIL is indicated for the treatment of patients with congestive heart failure who have not responded adequately to, or cannot be controlled by conventional therapy with diuretics and/or digitalis and in whom vasodilatation is indicated. BIO CAPTOPRIL has been used with diuretics and digitalis.

4.2 Posology and method of administration

Posology

Dosage must be individualised.

See section 4.4 regarding hypotension in salt and volume depleted patients.

BIO CAPTOPRIL should be taken one hour before food intake.

Hypertension

The initial dose of BIO CAPTOPRIL is 25 mg two or three times a day. If a satisfactory reduction of blood pressure has not been achieved after two weeks the dose of BIO CAPTOPRIL may be increased to 50 mg two or three times a day. If after an additional two weeks a further reduction in blood pressure is desirable, a diuretic may be added. For patients already receiving a diuretic, the initial dose of BIO CAPTOPRIL should be lower and administered with care.

The dose of BIO CAPTOPRIL in mild to moderate hypertension must not exceed 150 mg per day.

When BIO CAPTOPRIL is used alone, concomitant sodium restriction may be beneficial.

BIO CAPTOPRIL may be used advantageously in conjunction with other anti-hypertensive medicines.

Congestive heart failure

BIO CAPTOPRIL therapy must be started under close medical supervision. It should be added to conventional treatment with diuretic (and digitalis where indicated). A starting dose of 6,25 or 12,5 mg three times a day may minimise the duration of any transient hypotensive effect (see section 4.4). This dosage may be increased over a period of one to two weeks to 75 – 300 mg per day.

Patients with renal impairment

BIO CAPTOPRIL excretion is reduced in the presence of impaired renal function. After the desired therapeutic effect has been achieved the total daily dose should be reduce or the dose intervals increased. The following maximum daily doses are suggested as a guide to minimise medicine accumulation.

	Creatinine clearance (ml/min/1,75 m^3)	Maximum total daily dose (mg)
More than	80	300
	80 – 41	300
	40 – 21	150
	20 – 11	75
Less than	10	37,5

BIO CAPTOPRIL is removed by haemodialysis.

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

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to captopril or to any of the excipients of BIO CAPTOPRIL, listed in section 6.1.
- Patients with a history of angioedema related to previous treatment with an ACE-inhibitor or angiotensin receptor blocker: These patients should never again receive these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 ml/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Thiazide diuretics, in (fixed dose) combination with BIO-CAPTOPRIL, should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines (see section 4.5).
- Lithium therapy: Concomitant administration with BIO CAPTOPRIL may lead to toxic blood concentration of lithium (see section 4.5).
- Pregnancy and lactation (see sections 4.4 and 4.6).
- The concomitant use of BIO CAPTOPRIL with aliskerin-containing products is contraindicated (see sections

4.4 and 4.5).

- Concomitant use with sacubitril/valsartan therapy. BIO CAPTOPRIL must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving BIO-CAPTOPRIL, the treatment should be stopped promptly and switched to a different class of medicine (see sections 4.3 and 4.6). Should a woman contemplate pregnancy, the doctor should consider alternative medication.

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 producing effects ranging from relatively mild, such as cough (see section 4.4), to serious such as the following:

Head and neck angioedema

Severe life-threatening angioedema has been reported rarely with 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 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. Angioedema may occur with or without urticaria but usually the angioedema involves non-pitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes.

Angioedema of the extremities, face, lips, mucous membranes, tongue, glottis or larynx may occur in patients treated with BIO CAPTOPRIL particularly during the first weeks of treatment. However, in rare cases, severe angioedema may develop after long-term treatment with BIO CAPTOPRIL. Treatment should be discontinued promptly. In instances when swelling has been confined to the face and lips, the angioedema has generally resolved either without treatment or with antihistamines. Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be instituted. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

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 medicine of this class (see section 4.3).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of captopril. Treatment with captopril must not be initiated earlier than 36 hours after the last dose of sacubitril/ valsartan (see sections 4.3 and 4.5).

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

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 the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy or vildagliptin may be at increased risk for angioedema.

Anaphylactoid reactions during desensitisation

There have been rare reports of sustained life-threatening anaphylactoid reactions in patients undergoing desensitisation treatment with hymenoptera venom while receiving another ACE inhibitors, as contained in BIO CAPTOPRIL. In the same patients, these reactions were avoided when BIO CAPTOPRIL was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with BIO CAPTOPRIL, undergoing such desensitisation procedures.

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

Special precaution is advised in patients receiving BIO CAPTOPRIL as medications and undergoing haemodialysis with high-flux dialysis membranes (e.g., AN 69); particular to those having already shown similar reactions. Therefore, this combination should be avoided. In these patients, consideration should be given to use a different type of dialysis, membrane or a different class of medication.

Proteinuria

Proteinuria has been seen in patients receiving BIO-CAPTOPRIL, but this has been predominantly in those who had prior renal disease or in those receiving relatively high doses (in excess of 150 mg per day), or both. Alterations in renal function (as assessed by blood urea and serum creatinine) were infrequent in these patients and did not occur

in those who had prior renal disease. Nephrotic syndrome (hypoalbuminaemia, oedema and protein excretion greater than 3 g per day) has also occurred. In most cases, proteinuria subsided or cleared within 6 months whether or not BIO CAPTOPRIL 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 BIO CAPTOPRIL has not been established since pre-treatment biopsies were not taken and membranous glomerulopathy has been shown to occur in hypertensive patients not receiving BIO CAPTOPRIL.

A clinical study indicated that in 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.

For patients with prior renal disease or those receiving BIO CAPTOPRIL at doses greater than 150 mg per day, urinary protein estimations (dipsticks) should be done prior to treatment and monthly during the first 9 months of therapy. If this show increasing amount of urinary protein, a 24 hour quantitative determination of urinary protein should be done. If this exceeds one gram per day, the benefits and risks of continuing BIO CAPTOPRIL should be evaluated, and periodically thereafter.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, as contained in BIO-CAPTOPRIL. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely.

Neutropenia has occurred in some patients receiving BIO CAPTOPRIL especially in those who had pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy, or a combination of these

complicating factors.

It has been reported in clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1,6 mg/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 1,6 mg/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 (e.g., BIO CAPTOPRIL) has been associated with neutropenia.

In patients with collagen vascular disease (e.g., systemic lupus erythematosus, scleroderma), particularly those with co-existing renal impairment, BIO CAPTOPRIL 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 BIO CAPTOPRIL 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 medicines 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 BIO CAPTOPRIL should be told to report any signs of infection (e.g., 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 BIO-CAPTOPRIL 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 BIO CAPTOPRIL is used in patients with impaired renal function, collagen vascular disease, or who are receiving immunosuppressant medicines, 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 BIO CAPTOPRIL and other medicines has generally led to prompt return of the white cell count to normal, upon confirmation of neutropenia (neutrophil count < 1 000/mm^3) the medical practitioner should withdraw BIO CAPTOPRIL and closely follow the patient's course.
Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia and decreased

numbers of megakaryocytes.

Anaemia

Anaemia with reduced haemoglobin level was reported in renal transplant or haemodialysis patient. The reaction was greater in patients with higher baseline levels. Anaemia does not appear to be dose-dependent, however it is linked to ACE inhibitors mechanism of action. It is reversible upon BIO-CAPTOPRIL discontinuation.

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, dietary salt restrictions, vomiting or diarrhoea, and in patients undergoing dialysis (see sections 4.4, 4.5 and 4.8). Volume and/ or sodium depletion should be corrected before the administration of an ACE inhibitor and a lower starting dose should be considered.

Patients already on diuretic therapy may occasionally experience dizziness or light-headedness or, indicative of hypotension that may occur within one hour of the first dose. In patients who are receiving aggressive diuretic therapy, particularly those with either severe renin dependant hypertension (e.g., renovascular hypertension or severe congestive heart failure), exaggerate hypotensive responses have occurred, again usually within one hour of the initial dose of captopril. The possibility of this occurrence can be lessened in these patients by discontinuing diuretic therapy or significantly reducing the diuretic dose for 4 to 7 days prior to initiating BIO CAPTOPRIL (refer to section 4.5). By commencing captopril therapy with small doses (6,25 or 12,5 mg) the duration of any hypotensive effect is reduced.

In heart failure, where blood pressure was either normal or low, decreases in mean blood pressure greater than 20 %

were recorded in about half of the patients. This transient fall in blood pressure 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 dysrhythmia or conduction defects. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of BIO CAPTOPRIL or diuretic or both is increased. Hypotension was the reason for discontinuation of BIO CAPTOPRIL 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 BIO CAPTOPRIL. Of possible concern in patients with aortic and mitral valve 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 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 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 stabilises within a week or two, and generally returns to pre-treatment levels, without a decrease in therapeutic efficacy, within two months.

Hyperkalaemia

Since BIO CAPTOPRIL decreased aldosterone production, elevations in serum potassium have been observed in some patients treated with ACE inhibitors, as contained in BIO-CAPTOPRIL. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics (spironolactone, triamterene and amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g., ciclosporin, heparin, trimethoprim containing medicine). If concomitant use of the abovementioned medicines is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Cough

A persistent dry (non-productive) cough has been reported with the use of BIO CAPTOPRIL and appears to be a class-effect. The cough, which may be due to increased bronchial reactivity, appears to be more frequent 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 caused by increased bronchial reactivity attributed 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 medicines 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.

Use in diabetic nephropathy

In managing a patient with microalbuminuria, the medical practitioner 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 medical practitioner should also alert normotensive patients with diabetic nephropathy to the possibility of the rare occurrence of hypotension during treatment with BIO CAPTOPRIL.

Surgery/ Anaesthesia

In patients undergoing major surgery, or during anaesthesia with medicines which produce hypotension, BIO CAPTOPRIL will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion (see section 4.5).

Renovascular hypertension

Some patients with renal disease, particularly those with bilateral renal artery stenosis, have developed increases in blood urea and serum creatinine after reduction of blood pressure with BIO-CAPTOPRIL, usually along with a diuretic. BIO CAPTOPRIL dosage reduction or discontinuation of a diuretic, or both may be required. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion. Some

patients with heart failure have experience a reduction in renal function during long term treatment.

Hepatic impairment

Rarely, ACE inhibitors, as contained in BIO CAPTOPRIL 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 BIO CAPTOPRIL who develop jaundice or marked elevations of hepatic enzymes should discontinue the BIO CAPTOPRIL and receive appropriate medical follow-up.

Renal impairment

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 BIO CAPTOPRIL (captopril), usually in conjunction with a diuretic. BIO CAPTOPRIL (captopril) dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion; 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. BIO CAPTOPRIL should not be used in such patients (see section 4.3).

Evaluation of the hypertensive patients should always include assessment of renal function (see section 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 medicine 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.

The incidence of adverse reactions to captopril is principally associated with renal function since the BIO CAPTOPRIL is excreted primarily by the kidney. In cases of renal impairment (creatinine clearance ≤ 40 ml/min), the initial dosage of BIO CAPTOPRIL must be adjusted according to the patient's creatinine clearance (see section 4.2), and then as a function of the patient's response to treatment. The dose should not exceed that necessary for adequate control and should be reduced in patients with impaired renal function.

BIO CAPTOPRIL is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Aortic and mitral valve stenosis/ Obstructive hypertropic cardiomyopathy

BIO CAPTOPRIL should not be used in patients with aortic stenosis because of the potentially harmful consequences of reduced coronary perfusion secondary to the reduced blood pressure (see section 4.3). The use of BIO CAPTOPRIL should be avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Clinical chemistry

BIO CAPTOPRIL may cause a false-positive urine test of acetone (see section 4.5).

Dual blockade of the Renin-Angiotensin-aldosterone System (RAAS)

There is evidence that the concomitant use of ACE-inhibitors as contained in BIO-CAPTOPRIL, angiotensin II receptor blockers or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of BIO CAPTOPRIL and aliskiren is therefore contraindicated (see sections 4.3 and 4.5).

BIO CAPTOPRIL should not be used concomitantly with aliskiren (see section 4.3).

Lithium

The combination of lithium and BIO CAPTOPRIL is not recommended (see sections 4.3 and 4.5).

Diabetic patients

The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic medicines or insulin, namely during the first month of treatment with BIO CAPTOPRIL.

Lactose

BIO CAPTOPRIL contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take BIO CAPTOPRIL.

Paediatric population

Safety and effectiveness in individuals less than 18 years of age have not been established.

4.5 Interaction with other medicines and other forms of interaction

Surgery/Anaesthesia: In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, BIO CAPTOPRIL will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion (see section 4.4).

Medicines having vasodilator activity: Data on the effect of concomitant use of other vasodilators in patients receiving BIO CAPTOPRIL for heart failure are not available; therefore, nitroglycerine, other nitrates (such as minoxidil) (as used for management of angina) or other medicines having vasodilator activity should, if possible, be discontinued before starting BIO CAPTOPRIL (see section 4.4). If resumed during BIO CAPTOPRIL therapy, such medicines should be administered cautiously and perhaps at low dosage.

Haemodialysis membranes: Hypersensitivity-like (anaphylactoid) reactions have been reported with high-flux dialysis membranes (see section 4.4).

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

Diuretics (thiazide or loop diuretics): When a diuretic is added to the therapy of a patient receiving BIO 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 BIO CAPTOPRIL (see section 4.4). The hypotensive effects can be reduced by discontinuation the diuretic, by increasing volume or salt intake prior to commencing ACE inhibitor therapy. If it is not possible to discontinue the diuretic, the starting dose of BIO 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.

Potassium sparing diuretics or potassium supplements: ACE inhibitors, as contained in BIO CAPTOPRIL, attenuate diuretic induced potassium loss. Potassium-sparing diuretics (triamterene, amiloride and spironolactone), potassium-containing salt substitutes or potassium supplements may cause significant increase in serum potassium. If concomitant use is indicted because demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see section 4.4). Salt substitutes containing potassium or other medicines

associated with increases in serum potassium (e.g., trimethoprim containing medicines, ciclosporin, heparin) should also be used with caution.

Non-steroidal anti-inflammatory drugs: It has been described that non-steroidal anti-inflammatory drug (NSAIDs such as indomethacin, ibuprofen and including COX-2 inhibitor) and BIO CAPTOPRIL exert an additive effect on the increase in serum potassium, and may increase the risk of renal impairment. These effects are, in principle, reversible. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy, and periodically thereafter. Chronic administration of NSAIDs may reduce the antihypertensive effect of BIO CAPTOPRIL especially in cases of low renin hypertension. Other non-steroidal anti-inflammatory medicines (e.g., aspirin) may also have this effect.

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. Further, concomitant administration of the two classes of medicines may increase the risk of hyperkalaemia.

Lithium: Increased serum lithium levels and symptoms of lithium nephrotoxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy such as BIO CAPTOPRIL. These medicines should be co-administered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity (see section 4.3 and section 4.4).

Tricyclic antidepressants/antipsychotics, neuroleptics, amifostine, baclofen: Co-administration of BIO CAPTOPRIL with these medicines may enhance the hypotensive effects and the risk of postural hypotension.

Other antihypertensive medicines: BIO CAPTOPRIL has been safely co-administered with other commonly used anti-hypertensive medicines (e.g., beta-blockers and long-acting calcium channel blockers). Concomitant use of these medicines may increase the hypotensive effects of BIO-CAPTOPRIL.

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

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

Allopurinol, procainamide, cytostatic or immunosuppressive medicines: Concomitant administration with BIO CAPTOPRIL may lead to an increased risk for leukopenia especially when the latter are used at higher than currently recommended doses (see section 4.4).

Probenecid: The renal clearance of BIO CAPTOPRIL is reduced in the presence of probenecid.

Antidiabetics: ACE inhibitors, as contained in BIO CAPTOPRIL, can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics such as sulphonylurea in diabetics. Should this very rare interaction occur, it may be necessary to reduce the dose of the antidiabetic during simultaneous treatment with BIO CAPTOPRIL (see section 4.4).

Clinical chemistry: Captopril may cause a false-positive urine test for acetone (see section 4.4).

Dual blockade of the Renin-Angiotensin-aldosterone System (RAAS): Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, as contained in BIO-CAPTOPRIL, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function compared to monotherapy (see sections 4.3 and 4.4). Most patients receiving the combination of two RAAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients using captopril in combination with other medicines that block RAAS.

Mammalian Target of Rapamycin (mTOR) Inhibitors: Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see section 4.4).

Vildagliptin: Patients taking concomitant vildagliptin therapy may be at increased risk for angioedema.

Sacubitril/ valsartan: Concomitant use of ACE inhibitors such as BIO CAPTOPRIL with sacubitril/ valsartan is contraindicated as this increases the risk of angioedema.

Gold: In rare cases, nitritoid reactions with symptoms such as flushing, dizziness, nausea, vomiting and drop in blood pressure up to circulatory collapse have been observed in patients treated with ACE inhibitors and injectable gold preparations (sodium aurothiomalate) at the same time.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of BIO CAPTOPRIL is contraindicated during pregnancy. Pregnant women should be informed of the

potential hazards to the foetus and must not take BIO CAPTOPRIL during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with BIO CAPTOPRIL should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors, as contained in BIO CAPTOPRIL, during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/ or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spins bifida) and of kidney malformations.

BIO CAPTOPRIL passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of BIO CAPTOPRIL during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Breastfeeding

The use of BIO CAPTOPRIL is contraindicated during breastfeeding (see section 4.3)

4.7 Effects on ability to drive and use machines

The ability to drive and use machines may be reduced, namely at the start of the treatment, or when dosage is modified, and when used in combination with alcohol.

There have been no studies performed to investigate the effect of BIO CAPTORIL on driving performance or the

ability to operate machinery. However, BIO CAPTORIL may cause dizziness, drowsiness and disturbed vision which may influence the ability to drive and use machines (see section 4.8).

Patients should not drive or use machines until they have determined how they are affected.

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Blood and lymphatic disorders		Neutropenia/ agranulocytosis**, pancytopenia particularly in patients with renal dysfunction**, anaemia, thrombocytopenia, reversible lymphadenopathy, eosinophilia, auto-immune diseases and/or positive ANA-titres, serum sickness-like syndrome.	
Immune system disorders			Anaphylactoid reactions
Metabolism and	Weight loss (associated	Anorexia,	

nutrition disorders	with loss of taste).	hyperkalaemia, hypoglycaemia**, hyponatraemia particularly in patients receiving a low sodium diet or concomitant diuretics.	
Psychiatric disorders	Sleep disorders, insomnia	Confusion, depression.	
Nervous system disorders	Dysgeusia, reversible and self-limiting taste impairment, dizziness	Drowsiness, paraesthesia, headache, cerebrovascular accident/ insuffiency, including stroke, and syncope.	Ataxia*, nervousness*, somnolence*.
Eye disorders		Blurred vision, disturbed vision, itching and/or dry eyes.	
Cardiac disorders		Tachycardia, chest pain, dysrhythmia, angina pectoris, myocardial infarction, congestive heart failure, palpitations, cardiac arrest, cardiogenic	

		shock.	
Vascular disorders	Hypotension**	Raynaud syndrome, flush, pallor, orthostatic hypotension.	
Respiratory, thoracic and mediastinal disorders	Dry, irritating (non-productive) cough** and dyspnoea.	Bronchospasm, rhinitis, allergic alveolitis/ eosinophilic pneumonia.	A syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR. *
Gastrointestinal disorders	Nausea, vomiting, gastric irritations, abdominal pain diarrhoea, constipation, dry mouth.	Stomatitis resembling aphthous ulcerations, mouth ulcers, loss of appetite, tongue ulceration, glossitis, peptic ulcer, scalded sensation of the oral mucosa, pancreatitis, intestinal angioedema.	
Hepato-biliary disorders		Impaired hepatic function	

		and cholestasis (including jaundice), hepatitis including necrosis, elevated liver transaminase, alkaline phosphatase enzymes and serum bilirubin.	
Skin and subcutaneous tissue disorders	Pruritus with or without rash, rash, alopecia.	Angioedema involving extremities, face, lips, mucous membranes, tongue, glottis or larynx**, urticaria, Stevens Johnson syndrome, erythema multiforme, photosensitivity, erythroderma, bullous pemphigus and exfoliative dermatitis.	
Musculoskeletal, connective tissue disorders		Myalgia, arthralgia.	Myasthenia*
Renal and urinary disorders		Proteinuria**, renal insufficiency, acute	

		renal failure, polyuria, oliguria**, increased urine frequency, nephrotic syndrome, glomerulopathy.	
Reproductive system and breast disorders		Impotence, gynaecomastia, loss of libido	
General disorders and administration site conditions		Fatigue, malaise, fever, asthenia.	
Investigations		Increase of serum potassium, decrease of serum sodium, elevation of blood urea, serum creatinine and serum bilirubin, decreases in haemoglobin, haematocrit, leucocytes, thrombocytes, positive ANA-titre, elevated ESR.	

* Post-marketing experience

** See section 4.4

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/ risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

Measures to prevent absorption (e.g. administration of adsorbents and sodium sulphate within 30 minutes after intake) and hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementations should be given rapidly. Treatment with angiotensin-II should be considered. Bradycardia or extension vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered.

BIO CAPTOPRIL is removed by haemodialysis. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A. 7.1 Vasodilators, hypotensive medicine

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors, plain, ATC code: C09AA01

The mechanism of action of captopril is thought to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the medicine.

Renin, an enzyme synthesised by the kidneys is released into the circulation where it acts on plasma globulin substrate to produce angiotensin I, a relative 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 form the adrenal cortex, thereby contributing to sodium and fluid retention and potassium loss.

5.2 Pharmacokinetic properties

Absorption

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ace and this is reflected by a decrease in the pressor substance, angiotensin II, and an 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. As a result, small increases in serum potassium may occur along with sodium and fluid loss. Following oral administration of captopril rapid absorption occurs with peak blood levels at about one hour. The average minimal absorption is approximately 75 %. The presence of food in the gastro-intestinal tract reduces absorption by about 30 to 40 %. only 25 to 30 % of the medicine is bound to plasma proteins.

Elimination

About 75 % of a dose of captopril is excreted in the urine (of which 50 % is unchanged medicine and the remainder conjugates with endogenous thiol compounds (e.g., captopril cysteine and the disulphide dimer of the parent compound).

Captopril produces a reduction in peripheral arterial resistance in hypertensive patients with either no change or an increase in cardiac output.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Lactose anhydrous

Microcrystalline cellulose

Palmitic acid

Starch

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C, in a dry place. Protect from moisture and light.

6.5 Nature and contents of container

BIO CAPTOPRIL12,5 mg is packed in securitainers with 100 tablets.

BIO CAPTOPRIL25 mg is packed in securitainers with 60 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Block K West, Central Park

400 16th Road

Halfway House**,** Midrand

1685

8 REGISTRATION NUMBER(S)

BIO CAPTOPRIL12,5 mg: 31/7.1/0657

BIO CAPTOPRIL25 mg: 31/7.1/0658

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of Registration

BIO-CAPTOPRIL 12,5 mg: 27 July 1998

BIO-CAPTOPRIL 25 mg: 18 February 1998

10 DATE OF REVISION OF THE TEXT

01 June 2023