Coversyl® Plus

SCHEDULING STATUS: S3

1. NAME OF MEDICINE

Coversyl® Plus, tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg of perindopril tert-butylamine salt and 1,25 mg of indapamide.

Excipient with known effect: 61,55 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, 8-mm x 4-mm rod-shaped tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Coversyl® Plus is indicated for the treatment of essential hypertension, in patients where blood pressure is not adequately controlled and where fixed combination is considered more appropriate than monotherapy.

4.2 Posology and method of administration

Posology

The dosage regimen depends upon the individual requirements of the patient and is at the discretion of the medical doctor. One **Coversyl® Plus** tablet per day as a single dose, preferably to be taken in the morning before a meal.

Special populations

Elderly (see section 4.4):

It is recommended to start the treatment with only one of the constituents.

Patients with renal failure (see section 4.4):

In cases of severe renal failure (creatinine clearance below 30 ml/min), treatment is contra-indicated. In patients with a creatinine clearance greater than or equal to 30 ml/min and less than 60 ml/min, it is recommended to start the treatment with only one of the constituents. It is not necessary to change the dose when the creatinine clearance is greater than 60 ml/min.

Method of administration

Oral use.

4.3 Contraindications

This medicine is contraindicated in the following circumstances:

Linked to indapamide:

- Hypersensitivity to any of the ingredients of **Coversyl® Plus** or any other ACE-inhibitor.
- A history of angioedema related to previous therapy with ACE-inhibitors or angiotensin receptor blockers (ARBs): these patients must never again be given these medicines. (see section 4.4) ,
- Hereditary or idiopathic angioedema,
- Hypertrophic obstructive cardiomyopathy (HOCM),
- Severe renal function impairment (creatinine clearance below 30 ml/min),
- Bilateral renal artery stenosis,

- Renal artery stenosis in patients with a single kidney,
- Aortic stenosis (see WARNINGS AND SPECIAL PRECAUTIONS),
- Concomitant therapy with potassium-sparing diuretics (such as spironolactone, triamterene, amiloride (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS),
- Porphyria,
- Lithium therapy: concomitant administration with **Coversyl® Plus** may lead to toxic blood concentration of lithium (see section 4.5) ,
- Concomitant use of **Coversyl® Plus** with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73 m²) (see section 4.4 and 4.5). ,
- Concomitant use with sacubitril/valsartan (see section 4.4 and 4.5). ,
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5). ,
- Concomitant use of fluoroquinolones with ACE-inhibitors/Renin angiotensin receptor blockers is contraindicated in patients with moderate to severe renal failure (Creatinine Clearance ≤ 30 ml/min) and in elderly patients.
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4) ,
- Pregnancy and lactation (see section 4.4 and 4.6) ,

Linked to indapamide:

- Hypersensitivity to the active substance or to any other sulphonamides,
- Severe renal impairment (creatinine clearance below 30 ml/min),
- Hepatic encephalopathy,
- Severe hepatic impairment,
- Hypokalaemia,

- As a general rule, this medicine is inadvisable in combination with non antidysrhythmic agents causing *torsades de pointes* (see section 4.5)
- Lactation (section 4.6).

Linked to **Coversyl® Plus**

- Hypersensitivity to any of the excipients listed in section 6.1

Due to the lack of sufficient therapeutic experience, **Coversyl® Plus** should not be used in:

- Dialysis patients
- Patients with untreated decompensated heart failure.

4.4 Special warnings and precautions Special warnings

Common to perindopril and indapamide:

Lithium:

The combination of lithium with the combination of perindopril and indapamide is usually not recommended (see section 4.5).

Linked to perindopril:

Should a woman become pregnant while receiving **Coversyl® Plus**, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren may increases the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **Coversyl® Plus and** aliskiren is therefore contraindicated (see section 4.3 and 4.5). If dual blockade therapy is considered absolutely necessary, this

should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Potassium-sparing medicines, potassium supplements or potassium-containing salt substitutes:

The combination of perindopril and potassium-sparing medicines, potassium supplements or potassium-containing salt substitutes is usually not recommended (see section 4.5).

Risk of neutropenia/agranulocytosis/thrombocytopenia/anaemia in immuno-suppressed patients:

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors. In patients with normal renal function and no other complicating factors, neutropenia rarely occurs. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodical monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever) (see section 4.5 and 4.8).

Renovascular hypertension:

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE-inhibitors (see section 4.3). Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Hypersensitivity/Angioneurotic Oedema:

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has rarely been reported in patients receiving treatment with ACE-inhibitors, including perindopril (see section 4.8). This may occur at any time during treatment. In such cases, treatment with **Coversyl® Plus** should immediately be stopped and the patient should be monitored until the oedema has disappeared. Angioneurotic oedema combined with laryngeal oedema may be fatal. Involvement of tongue, glottis or larynx may lead to an obstruction of the airways. A subcutaneous injection of adrenaline (epinephrine) at 1:1 000 (0,3 ml to 0,5 ml) should be administered quickly and other appropriate measures taken. The prescribing of **Coversyl® Plus** or any other ACE-inhibitor is then contraindicated in these patients (see section 4.3).

Black patients receiving ACE-inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a previous history of angioneurotic oedema, which was not linked to taking an ACE-inhibitor, have an increased risk of angioneurotic oedema with **Coversyl® Plus** (see section 4.3).

Intestinal angioedema has rarely been reported 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 facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or with 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.

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):

Patients concomitantly taking mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at an increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3).

Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see section 4.3 and 4.5). Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE-inhibitors may also increase the risk of angioedema (see section 4.5). Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment, with

fluoroquinolones or ACE-inhibitors/Renin angiotensin receptor blockers whether used separately or concomitantly.

Anaphylactoid reactions during desensitisation:

There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE-inhibitors during desensitisation treatment with hymenoptera (bees, wasps) venom. **Coversyl® Plus** should be used with caution in allergic patients treated with desensitisation, and avoided in those undergoing venom immunotherapy. However, these reactions could be prevented by temporary withdrawal of **Coversyl® Plus** for at least 24 hours before treatment in patients who require both ACE-inhibitors and desensitisation.

Anaphylactoid reactions during Low Density Lipoprotein (LDL) apheresis:

There have been reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE-inhibitors during low-density lipoprotein apheresis with dextran sulphate adsorption. **Coversyl® Plus** should be avoided in such patients. However, these reactions could be prevented by temporary withdrawal of **Coversyl® Plus** for at least 24 hours before treatment in patients who require both ACE-inhibitors and LDL apheresis.

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE-inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Primary aldosteronism:

Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive medication acting through inhibition of the renin-angiotensin system. Therefore, the use **Coversyl® Plus** is not recommended.

Linked to indapamide:

Hepatic encephalopathy:

When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause hepatic encephalopathy. Administration of **Coversyl® Plus** should be stopped immediately if this occurs.

Photosensitivity:

Cases of photosensitivity reactions have been reported with thiazides and related thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Linked to Coversyl® Plus:

Renal insufficiency:

In cases of severe renal insufficiency (creatinine clearance < 30 ml/min), treatment is contraindicated (see section 4.3). In patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted with one constituent only.

In these patients usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months

during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.

Coversyl® Plus is usually not recommended in case of bilateral renal artery stenosis or a single functioning kidney.

Hypotension and water and electrolyte depletion:

There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore, systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhoea or vomiting. Regular monitoring of plasma electrolytes should be carried out in such patients. Marked hypotension may require the implementation of an intravenous infusion of isotonic saline. Transient hypotension is not a contra-indication to continuation of treatment. After reestablishment of a satisfactory blood volume and blood pressure, treatment can be started again with only one of the constituents.

Potassium levels:

The combination of perindopril and indapamide does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. Regular monitoring of plasma potassium levels should be carried out.

Excipients

Coversyl® Plus should not be administered to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Linked to perindopril:

Cough:

A dry cough has been reported with the use of ACE-inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If the prescription of an ACE-inhibitor is still preferred, continuation of treatment may be considered.

Children:

The efficacy and safety of perindopril in children and adolescents, alone or in combination has not been established.

Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, etc.).

Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium-free diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites.

Blocking the renin-angiotensin-aldosterone system with an ACE-inhibitor may cause, particularly at the time of the first administration and during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency.

Occasionally this can be acute in onset, although rare, and with a variable time to onset. In such cases, the treatment should then be initiated with only one of the constituents and increased progressively.

Elderly:

Renal function and potassium levels should be tested before the start of treatment. The initial dose is subsequently adjusted according to blood pressure response, especially in cases of water and electrolyte depletion, in order to avoid sudden onset of hypotension.

Patients with known atherosclerosis:

The risk of hypotension exists in all patients, but particular care should be taken in patients with ischaemic heart disease or cerebral circulatory insufficiency, with treatment being started with only one of the constituents.

Renovascular hypertension:

The treatment of renovascular hypertension is revascularisation. Nonetheless, ACE-inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.

Treatment should be started in a hospital setting with only one of the constituents and renal function and potassium levels should be monitored, since some patients have developed a functional renal insufficiency, which was reversed when treatment was stopped.

Cardiac failure/severe cardiac insufficiency:

In patients with severe cardiac insufficiency (grade IV) or in patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with only one of the constituents. Treatment with beta-blockers in hypertensive patients with

coronary insufficiency should not be stopped: the ACE-inhibitor should be added to the beta-blocker.

Diabetic patients:

In patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose.

The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic medication or insulin, namely during the first month of treatment with an ACE-inhibitor (see section 4.5).

Ethnic differences:

As with other angiotensin converting enzyme inhibitors, perindopril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Surgery/anaesthesia:

Coversyl® Plus may precipitate hypotension during general anaesthesia. It is therefore recommended that treatment with perindopril should be discontinued where possible one day before surgery.

Aortic stenosis / hypertrophic cardiomyopathy:

ACE-inhibitors should be used with caution in patients with an obstruction in the outflow tract of the left ventricle.

Hepatic failure:

Coversyl® Plus has 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 **Coversyl® Plus** who develop jaundice or marked elevations of hepatic enzymes should discontinue **Coversyl® Plus** and receive appropriate medical follow-up (see section 4.8.)

Hyperkalaemia:

Elevations in serum potassium have been observed in some patients treated with ACE-inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g; spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole, other ACE-inhibitors, angiotensin-II receptor antagonists, acetylsalicylic acid ≥ 3 g/day, COX-2 inhibitors and non-selective NSAID's, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim).

The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal dysrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Linked to Indapamide:

Water and electrolyte balance:

Indapamide may cause electrolyte imbalances.

Sodium levels:

These should be tested before treatment is started, then at regular intervals. Indapamide treatment can cause a reduction in sodium levels, which may have serious consequences. Reduction in sodium levels can initially be asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients (see sections 4.8 and 4.9)

Hyponatraemia with hypovolaemia may be responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight.

Potassium levels:

Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide related diuretics. The risk of onset of lowered potassium levels (< 3,4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure. In such cases hypokalaemia increases the cardiac toxicity of cardiac glycosides and the risk of rhythm disorders.

Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic.

Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe rhythm disorders, in particular *torsades de pointes*, which may be fatal.

In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment. If low potassium levels are detected, correction is required.

Calcium levels:

Thiazide diuretics and thiazide related diuretics may reduce the urinary excretion of calcium and cause a mild and transient increase in plasma calcium levels. Marked raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases treatment should be stopped before investigating the parathyroid function.

Blood glucose:

Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

Uric acid:

Tendency to gout attacks may be increased in hyperuricaemic patients.

Renal function and diuretics:

Thiazide diuretics and thiazide-related diuretics are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25 mg/l, i.e. 220 µmol/l for an adult).

In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient according to the Cockroft formula:

$$cl_{cr} = (140 - age) \times body\ weight / 0{,}814 \times plasma\ creatinine\ Level$$

with : age expressed in years

body weight in kg

plasma creatinine level in µmol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0,85.

Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function, but may however worsen a pre-existing renal insufficiency.

Acute myopia and secondary angle-closure glaucoma:

Sulphonamide or sulphonamide derivative medicines can cause an idiosyncratic reaction resulting in transient myopia and acute angle-closure glaucoma. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue the intake of the medication as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Athletes:

Athletes should be aware that this product contains indapamide, which may give a positive reaction in drug tests.

4.5 Interactions with other medicines and other forms of interaction

Linked to Coversyl® Plus:

Concomitant use not recommended:

Lithium:

An increase in lithium levels may occur. If the combination of an ACE-inhibitor and a potassium sparing diuretic is unavoidable, strict monitoring of lithium levels and adjustment of the dose are necessary (see sections 4.3 and 4.4).

Concomitant use which requires special care:

Baclofen:

Potentiation of antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

NSAID (systemic route), high-dose salicylates (including aspirin ≥ 3 g/day):

When ACE-inhibitors are simultaneously administered with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Concomitant use which requires some care:

Imipramine-like (tricyclic) antidepressants, neuroleptics:

Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Linked to perindopril:

Dual blockade of the RAAS with ARBs, ACE-inhibitors, or aliskiren:

Clinical trial data have shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see sections 4.3 and 4.4).

Medicines inducing hyperkalaemia:

Some medicines or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE-inhibitors, angiotensin-II receptor antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim. The combination of these medicines increases the risk of hyperkalaemia.

Concomitant use contraindicated (see section 4.3):

Aliskiren:

In diabetic or renal impaired patients, the risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increases.

Extracorporeal treatments:

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g.

polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Sacubitril/valsartan:

The concomitant use of perindopril with sacubitril/valsartan is contraindicated as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Concomitant use not recommended:

Aliskiren:

In patients other than diabetic or renal impaired patients, the risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increases (see section 4.4).

Concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker:

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with an ACE-inhibitor and an angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent.

Dual blockade (e.g. by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure (see section 4.4).

Estramustine:

Risk of increased adverse effects such as angioneurotic oedema (angioedema).

Co-trimoxazole (trimethoprim/sulfamethoxazole):

Patients concomitantly taking co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

Potassium-sparing diuretics (, triamterene, amiloride, potassium salts:

Increased levels of potassium (potentially lethal), particularly in cases of renal insufficiency (addition of potassium-sparing effects). Potassium-raising agents should not be combined with **Coversyl® Plus**, except when potassium levels are low. (see section 4.4). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see section “Concomitant use which requires special care”.

Concomitant use which requires special care:

Antidiabetic agents (insulin, hypoglycaemic sulphonamides):

The use of **Coversyl® Plus** may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides.

Non-potassium-sparing diuretics:

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE-inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

In arterial hypertension:

When prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE-inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE-inhibitor must be initiated with a low dosage and progressively increased.

In diuretic-treated congestive heart failure:

The ACE-inhibitor should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE-inhibitor therapy.

Potassium-sparing diuretics (eplerenone, spironolactone):

With eplerenone or spironolactone at doses between 12,5 mg to 50 mg per day and with low doses of ACE-inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40 %, and previously treated with ACE-inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-compliance with the prescription recommendations about this combination.

Before initiating the combination, check the absence of hyperkalaemia and renal impairment.

Close monitoring of potassium and creatinine is recommended in the first month of the treatment, once a week at the beginning and, monthly thereafter.

Racecadotril:

ACE-inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a product used against acute diarrhoea).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):

Patients concomitantly taking mTOR inhibitors therapy, may be at an increased risk for angioedema (see section 4.4).

Concomitant use which requires some care:

Antihypertensive agents and vasodilators:

Increase of the hypotensive effect of **Coversyl® Plus**. Concomitant use with nitroglycerin and other nitrates, or other vasodilatators, may further reduce blood pressure.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide:

Concomitant administration with **Coversyl® Plus** may lead to an increased risk for Leucopenia (see section 4.4).

Anaesthetic agents:

Coversyl® Plus may enhance the hypotensive effects of certain anaesthetic Medicines (see section 4.4).

Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin):

Increased risk of angio-oedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptin, in patients co-treated with an ACE-inhibitor.

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE-inhibitors.

Gold:

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have rarely been reported in patients on therapy with injectable gold (auranofin) and concomitant ACE-inhibitor therapy including perindopril.

Linked to indapamide:

Concomitant use that requires special care

Anti-dysrhythmic medication, which produce *torsades de pointes*: Class IA anti-dysrhythmic agents (quinidine, hydroquinidine, disopyramide), amiodarone, sotalol:

Due to the risk of hypokalaemia, indapamide should be administered with caution when associated with medicines that induced *torsades de pointes* such as class IA antiarrhythmic agents (quinidine, hydroquinidine, disopyramide); class III antiarrhythmic agents (amiodarone, dofetilide, ibutilide, bretylium, sotalol); some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, sultopride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.

Potassium-lowering medicines: amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives:
Increased risk of low potassium levels (additive effect). Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with digitalis. Non stimulant laxatives should be used.
Torsades de pointes (low potassium levels are a risk factor, as are bradycardia and a pre-existing long QT interval). Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.

Digitalis preparations:
Low potassium levels favour the toxic effects of digitalis. Potassium levels and ECG should be monitored and treatment reconsidered if necessary.

Allopurinol:
Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Digitalis preparations:

Low potassium levels favour the toxic effects of digitalis.

Potassium levels and ECG should be monitored and treatment reconsidered if necessary.

Concomitant use which requires some care:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene):

Potassium levels and ECG should be monitored and treatment reconsidered if necessary. Whilst rational combinations are useful in some patients, hypokalaemia or hyperkalaemia (particularly in patients with renal failure or diabetes) may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin:

Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics. Do no use metformin when plasma creatinine levels exceed 15 mg/l (135 micromol/l) in men and 12 mg/l (110 micromol/l) in women.

Iodinated contrast media:

In cases of dehydration caused by indapamide, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used.

Rehydration should be carried out before the iodinated compound is administered.

Calcium (salts):

Risk of increased levels of calcium due to reduced elimination of calcium in the urine.

Ciclosporin (tacrolimus):

Risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no salt and water depletion.

Corticosteroids, tetracosactide (systemic route):

Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

4.6 Fertility, pregnancy and lactation

The use of **Coversyl® Plus** is contraindicated during pregnancy. Pregnant women should be informed of the potential harzards to the foetus and must not take **Coversyl® Plus** 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 **Coversyl® Plus** should be stopped and if appropriate, alternative therapy should be started.

Foetal exposure to ACE-inhibitors 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.

Coversyl® Plus 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 newborns have been reported after administration of ACE-inhibitors in the second and third trimester. Cases of skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Should exposure to ACE-inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE-inhibitors should be closely observed for hypotension (see also section 4.3).

Lactation

Coversyl® Plus is contraindicated during lactation.

Linked to perindopril:

Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Linked to indapamide:

There is insufficient information on the excretion of indapamide/metabolites in human milk. Hypersensitivity to sulfonamide-derived drugs and hypokalaemia might occur. A risk to the newborns/infants cannot be excluded.

Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decrease or even suppression of milk lactation.

Fertility

There was no effect on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines

Individual reactions related to a reduction in blood pressure may occur in some patients. As a result, the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

Summary of safety profile:

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide. Four percent of the patients on treatment with **Coversyl® Plus** experience hypokalaemia (potassium level < 3,4 mmol/l).

The most commonly reported adverse reactions observed are:

- with perindopril: dizziness, headache, paraesthesia, dysgeusia, visual impairment, vertigo, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, dyspepsia, diarrhoea, nausea, vomiting, pruritus, rash, muscle cramps and asthenia.
- with indapamide: hypersensitivity reaction, mainly dermatological, in subjects with predisposition to allergic and asthmatic reactions and maculopapular rashes.

Tabulated list of adverse reaction:

The following undesirable effects have been observed during clinical trials and/or post-marketing use and ranked under the following frequency:

Very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Perindopril	Indapamide
Infections and infestations	Rhinitis	Very rare	-
Blood and Lymphatic System Disorders	Eosinophilia	Uncommon*	-
	Agranulocytosis (see section 4.4)	Very rare	Very rare
	Aplastic anaemia	-	Very rare
	Pancytopenia	Very rare	-
	Leukopenia	Very rare	Very rare
	Neutropenia (see section 4.4)	Very rare	-
	Haemolytic anaemia	Very rare	Very rare
	Thrombocytopenia (see section 4.4)	Very rare	Very rare
Immune system disorders	Hypersensitivity (reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions)	-	Common
Metabolism and Nutrition Disorders	Hypoglycaemia (see sections 4.4 and 4.5)	Uncommon*	-
	Hyperkalaemia, reversible on discontinuation (see section 4.4)	Uncommon*	-
	Hyponatraemia (see section 4.4)	Uncommon*	Not known

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Perindopril	Indapamide
	Hypercalcaemia	-	Very rare
	Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see section 4.4)	-	Not known
Psychiatric Disorders	Mood altered	Uncommon	-
	Sleep disorder	Uncommon	-
	Confusion	Very rare	-
Nervous System Disorders	Dizziness	Common	-
	Headache	Common	Rare
	Paraesthesia	Common	Rare
	Dysgeusia	Common	-
	Somnolence	Uncommon*	-
	Syncope	Uncommon*	Not known
	Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	Very rare	-
	Possibility of onset of hepatic encephalopathy in case of	-	Not known

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Perindopril	Indapamide
	hepatic insufficiency (see sections 4.3 and 4.4)		
Eye Disorders	Visual impairment	Common	Not known
	Myopia (see section 4.4)	-	Not known
	Vision blurred	-	Not known
Ear and Labyrinth Disorders	Vertigo	Common	Rare
	Tinnitus	Common	-
Cardiac Disorders	Palpitations	Uncommon*	-
	Tachycardia	Uncommon*	-
	Angina pectoris (see section 4.4)	Very rare	-
	Dysrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation)	Very rare	Very rare
	Myocardial infarction possibly secondary to excessive hypotension in high risk patients (see section 4.4)	Very rare	-
	Torsade de pointes (potentially fatal) (see section 4.4 and 4.5)	-	Not known

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Perindopril	Indapamide
Vascular Disorders	Hypotension (and effects related to hypotension) (see section 4.4)	Common	Very rare
	Vasculitis	Uncommon*	-
	Raynaud's phenomenon	Unknown	
Respiratory, Thoracic and Mediastinal Disorders	Cough (see sections 4.4)	Common	-
	Dyspnoea	Common	-
	Bronchospasm	Uncommon	-
	Eosinophilic pneumonia	Very rare	-
Gastrointestinal Disorders	Abdominal pain	Common	-
	Constipation	Common	Rare
	Diarrhoea	Common	-
	Dyspepsia	Common	-
	Nausea	Common	Rare
	Vomiting	Common	Uncommon
	Dry mouth	Uncommon	Rare
	Pancreatitis	Very rare	Very rare
Hepatobiliary Disorders	Hepatitis (see section 4.4)	Very rare	Not known
	Hepatic function abnormal	-	Very rare

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Perindopril	Indapamide
Skin and Subcutaneous Tissue Disorders	Pruritus	Common	-
	Rash	Common	-
	Rash maculo-papular	-	Common
	Urticaria (see section 4.4)	Uncommon	Very rare
	Angioedema (see section 4.4)	Uncommon	Very rare
	Purpura	-	Uncommon
	Hyperhidrosis	Uncommon	-
	Photosensitivity reaction	Uncommon*	Not known
	Pemphigoid	Uncommon*	-
	Psoriasis aggravation	Rare*	-
	Erythema multiforme	Very rare	-
	Toxic epidermal necrolysis	-	Very rare
	Stevens Johnson syndrome	-	Very rare
Musculoskeletal and Connective Tissue Disorders	Muscle cramps	Common	-
	Possible worsening of pre-existing acute disseminated lupus erythematosus	-	Not known
	Arthralgia	Uncommon*	-
	Myalgia	Uncommon*	-

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Perindopril	Indapamide
Renal and Urinary Disorders	Renal insufficiency	Uncommon	-
	Renal failure acute	Very rare	Very rare
Reproductive System and Breast disorders	Erectile dysfunction	Uncommon	-
General Disorders and Administration Site Conditions	Asthenia	Common	-
	Chest pain	Uncommon*	-
	Malaise	Uncommon*	-
	Peripheral oedema	Uncommon*	-
	Pyrexia	Uncommon*	-
	Fatigue	-	Rare
Investigations	Blood urea increased	Uncommon*	-
	Blood creatinine increased	Uncommon*	-
	Blood bilirubin increased	Rare	-
	Hepatic enzyme increased	Rare	Not known
	Haemoglobin decreased and haematocrit decreased (see section 4.4)	Very rare	-
	Blood glucose increased	-	Not known

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Perindopril	**Indapamide**
	Blood uric acid increased	-	Not known
	Electrocardiogram QT prolonged (see sections 4.4 and 4.5)	-	Not known
Injury, Poisoning and Procedural Complications	Fall	Uncommon*	-

**Frequency calculated from clinical trials for adverse events detected from spontaneous report.*

Cases of Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) have been reported with other ACE-inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE-inhibitor therapy including perindopril.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The most likely adverse event in case of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria, which may progress to anuria (due to hypovolaemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.

The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal.

If marked hypotension occurs, this can be treated by placing the patients in a supine position with the head lowered. If necessary an IV infusion of isotonic saline may be given, or any other method of volaemic expansion may be used.

Perindoprilat, the active form of perindopril, can be dialysed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: perindopril and diuretic, plain, ATC code: C09B A04

Coversyl® Plus is a combination of perindopril tert-butylamine salt, an angiotensin-converting enzyme inhibitor (ACE-inhibitor), and indapamide, a chlorosulphamoyl diuretic. Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive.

Following oral administration the absorption of perindopril is rapid (peak concentration within 1 hour), and relatively complete (plasma-availability above 75 %). The peak concentration of perindoprilat, the active metabolite, is reached within 3 to 4 hours and peak pharmacological activity is obtained within 4 to 6 hours.

In terms of trough versus peak blood pressure effect, the trough effect ranges between 75 – 100 % of peak effects.

Perindopril and perindoprilat both have a low volume of distribution and plasma protein binding is weak. Perindoprilat binds to angiotensin converting enzyme at both plasma and tissue levels. Apart from active perindoprilat, perindopril gives rise to 5 metabolites, all of which are inactive. Perindopril is eliminated in the urine and

the half-life of its free fraction is approximately one hour. Breakdown of the bond between perindoprilat and the angiotensin-converting enzyme leads to a pharmacodynamic half-life of about 25 hours.

Indapamide, [N-(3-sulphamoyl-4-chlorobenzamido) 2-methyl indoline] is an indole derivative of chlorosulphonamide with an antihypertensive action. It has an extra-renal antihypertensive action resulting in a decrease in vascular hyper-reactivity and a reduction in total peripheral and arteriolar resistance. This action is thought to be due to the inhibition of transmembrane ionic influx, essentially calcic, and the stimulation of synthesis of the vasodilatory hypotensive prostaglandin PGE_2.

There is also a direct renal diuretic action.

Prolonged use of indapamide has been shown to be associated with a reduction in left ventricular mass in hypertensive patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate (E470B)

Colloidal hydrophobic silica

Microcrystalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

6.5 Nature and contents of container

Blister packs of clear PVC and Aluminium with 30 tablets in a carton.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Servier Laboratories South Africa (Pty) Ltd

Building Number 4

Country Club Estate

21 Woodlands Drive

Woodmead

2191

8. REGISTRATION NUMBER:

33/7.1.3/0363

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10. DATE OF REVISION OF THE TEXT

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