PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ACTI-PREX PLUS, tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

ACTI-PREX PLUS contains sugar (58,47 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

ACTI-PREX PLUS: White, rod shaped tablets having ‘P I’ debossed on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACTI-PREX PLUS is indicated for the treatment of essential hypertension, in patients where blood pressure is not adequately controlled and where a 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 ACTI-PREX 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 impairment (see section 4.4):

In cases of severe renal failure (creatinine clearance below 30 ml/min), treatment is contraindicated. 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

The use of ACTI-PREX PLUS is contraindicated in patients with:

- Known hypersensitivity to the active substances (perindopril tert-butylamine or indapamide), including any other ACE inhibitors, sulphonamides or to any of the excipients listed in section 6.1.
- Severe renal function impairment (creatinine clearance less than 30 ml/min).
- Due to a lack of sufficient therapeutic experience, ACTI-PREX PLUS should also not be used in dialysis patients and patients with untreated decompensated cardiac failure.

Linked to Perindopril

- A history of angioedema (for example Quincke's oedema) 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).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis (see section 4.4).
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene and amiloride (see section 4.4 and 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with ACTI-PREX PLUS may lead to toxic blood concentrations of lithium (see section 4.5).
- The concomitant use of ACTI-PREX PLUS with renin inhibitors, such as aliskiren is contraindicated 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. ACTI-PREX PLUS must not be initiated earlier than 36 hours after the last dose of 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

- Hepatic encephalopathy.
- Severe hepatic impairment.

- Hypokalaemia.
- As a general rule, ACTI-PREX PLUS is inadvisable in combination with non-antidysrhythmic medicines causing *torsades de pointes* (see section 4.5).
- Lactation (see section 4.6).

4.4 Special warnings and precautions for use

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

Linked to ACTI-PREX PLUS

Lithium:

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

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 the therapeutic stability period.

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

ACTI-PREX 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 contraindication to continuation of treatment. After re-establishment of a satisfactory blood volume and blood pressure, treatment can be started again either at a reduced dose or 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. As with any antihypertensive medicine in combination with a diuretic, regular monitoring of plasma potassium levels should be carried out.

Excipients

ACTI-PREX PLUS contains lactose and should therefore not be administered to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

<u>Linked to perindopril</u>

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

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers (ARBs) or aliskrien may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACTI-PREX PLUS and renin inhibitors such as 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 are usually not recommended (see section 4.5).

Risk of neutropenia/agranulocytosis/thrombocytopenia/anaemia in immunosuppressed 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 (e.g. systemic lupus erythematosus and scleroderma), 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.

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.

Hypersensitivity/angioneurotic oedema

Angioneurotic oedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during treatment. In such cases, treatment with ACTI-PREX PLUS should be stopped immediately and the patient should be monitored until the oedema has disappeared.

Angioneurotic oedema combined with laryngeal oedema may be fatal. Involvement of the tongue, glottis or larynx may lead to an obstruction of the airways. A subcutaneous injection of adrenaline (epinephrine) at 1:1000 (0,3 ml to 0,5 ml) should be administered quickly and other appropriate measures taken. The prescribing of ACTI-PREX 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 history of angioneurotic oedema, unrelated to ACE inhibitor therapy, may be at increased risk of angioneurotic oedema while receiving ACTI-PREX 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. ACTI-PREX PLUS should be used with caution in allergic patients treated with desensitisation and avoided in those undergoing venom immunotherapies. However, these reactions could be prevented by temporary withdrawal of ACTI-PREX PLUS for at least 24 hours before treatment in patients who require both ACE inhibitors and desensitisation.

Anaphylactoid reactions during low-density lipoproteins (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. ACTI-PREX PLUS should be avoided in these patients. These reactions can be prevented by temporary withdrawal of ACTI-PREX 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 medicine.

Primary aldosteronism

Patients with primary hyperaldosteronism generally will not respond to antihypertensive medication acting through inhibition of the renin-angiotensin system. Therefore, the use ACTI-PREX PLUS is not recommended.

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 angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be considered.

Paediatric population

The efficacy and tolerability of perindopril in children and adolescents, alone or in a combination, have not been established.

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

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 at a lower dose and increased progressively.

Elderly

Renal function and potassium levels should be tested before the start of the 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.

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

ACTI-PREX PLUS may precipitate hypotension during general anaesthesia.

It is therefore recommended that treatment with long-acting angiotensin converting enzyme inhibitors such as 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 of the left ventricle.

Hepatic failure

ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACTI-PREX PLUS who develop jaundice or marked elevations of hepatic enzymes should discontinue ACTI-PREX 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, inter-current 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 medicines 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 medicines is deemed appropriate they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Linked to indapamide

Hepatic encephalopathy

When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause hepatic encephalopathy. Administration of ACTI-PREX 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.

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 urinary excretion of calcium and cause a mild and transient increase in plasma calcium levels. Markedly raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases the 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:

clcr = (140 - age) x body weight / 0,814 x 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 impairment.

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 note that this product contains an active substance which may cause a positive reaction in doping tests.

4.5 Interaction with other medicines and other forms of interaction

Linked to ACTI-PREX 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. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

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

When ACE-inhibitors are administered simultaneously 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, renin 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 renin inhibitors such as aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see section 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 medicines 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 medicine.

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:

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 medicine.

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 (spironolactone, triamterene, alone or in combination), potassium supplements or potassium containing salts substitutes

Increased levels of potassium (potentially lethal), particularly in cases of renal insufficiency (addition of potassium-sparing effects). Potassium-raising medicines should not be combined with ACTI-PREX 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 medicines (insulin, hypoglycaemic sulphonamides)

The use of ACTI-PREX 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 reintroduced thereafter, 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 medicines and vasodilators

Increase of the hypotensive effect of ACTI-PREX PLUS. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Allopurinol, cytostatic or immunosuppressive medicines, systemic corticosteroids or procainamide

Concomitant administration with ACTI-PREX PLUS may lead to an increased risk of leucopenia (see section 4.4).

Anaesthetic medicines

ACTI-PREX 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 been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) 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 antidysrhythmic medicines (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 antidysrhythmic medicines (quinidine, hydroquinidine, disopyramide); class III antidysrhythmic medicines (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 cardiac 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.

Concomitant use which requires some care:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene)

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 not use metformin when plasma creatinine levels exceed 15 mg/l (135 µmol/l) in men and 12 mg/l (110 µmol/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

Pregnancy

The use of ACTI-PREX PLUS is contraindicated during pregnancy.

Linked to perindopril

Pregnant women should be informed of the potential hazards to the foetus and must not take ACTI-PREX 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 ACTI-PREX PLUS should be stopped immediately 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, spina bifida) and of kidney malformations.

ACTI-PREX PLUS passes through the placenta and can 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 such as in ACTI-PREX PLUS 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).

Should exposure to ACE inhibitors 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 section 4.3).

Linked to indapamide

Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a foeto-placental ischaemia and growth retardation.

Breastfeeding

ACTI-PREX PLUS is contraindicated during breastfeeding.

Linked to perindopril

Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended.

Linked to indapamide

Indapamide is contraindicated during breastfeeding.

Fertility

No effect on reproductive performance or fertility is anticipated.

4.7 Effects on ability to drive and use machines

Dizzines may be experienced. As a result, the ability to drive or operate machines 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.

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.

List of adverse reactions

Infections and infestations:

Less frequent: Rhinitis.

Blood and lymphatic system disorders:

Less frequent: Eosinophilia, agranulocytosis (see section 4.4), aplastic anaemia, pancytopenia, leukopenia, neutropenia (see section 4.4), haemolytic anaemia, thrombocytopenia (see section 4.4).

Immune system disorders:

Frequent: Hypersensitivity (reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions).

Metabolism and nutrition disorders:

Less frequent: Hypoglycaemia (see section 4.4 and 4.5), hyperkalaemia, reversible on discontinuation (see section 4.4), hyponatraemia (see section 4.4), hypercalcaemia.

Frequency unknown: Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see section 4.4).

Psychiatric disorders:

Less frequent: Altered mood, sleep disorder, confusion.

Nervous system disorders:

Frequent:	Dizziness, headache, paraesthesia, headache, dysgeusia.
Less frequent:	Somnolence, syncope, stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Frequency unknown:	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see section 4.3 and 4.4).

Eye disorders:

Frequent:	Vision disturbance.
Frequency unknown:	Myopia (see section 4.4), blurred vision.

Ear and labyrinth disorders:

Frequent:	Vertigo, tinnitus.

Cardiac disorders:

Less frequent:	Palpitations, tachycardia, angina pectoris (see section 4.4), dysrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation), myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Frequency unknown:	*Torsade de pointes* (potentially fatal) (see sections 4.4 and 4.5).

Vascular disorders:

Frequent:	Hypotension (and effects related to hypotension (see section 4.4).
Less frequent:	Vasculitis.
Frequency unknown:	Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders:

Frequent: Cough, dyspnoea.

Less frequent: Bronchospasm, eosinophilic pneumonia.

Gastrointestinal disorders:

Frequent: Abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting.

Less frequent: Dry mouth, pancreatitis.

Hepatobiliary disorders:

Less frequent: Hepatitis (see section 4.4), abnormal hepatic function.

Skin and subcutaneous tissue disorders:

Frequent: Pruritus, rash, rash maculo-papular.

Less frequent: Urticaria (see section 4.4), angioedema (see section 4.4), purpura, hyperhidrosis, photosensitivity reaction, pemphigoid, psoriasis aggravation, erythema multiforme, toxic epidermal necrolysis, Stevens Johnson syndrome.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Muscle cramps.

Less frequent: Arthralgia, myalgia.

Frequency unknown: Possible worsening of pre-existing acute disseminated lupus erythematosus.

Renal and urinary disorders:

Less frequent: Renal insufficiency, acute renal failure.

Reproductive system and breast disorders

Less frequent: Erectile dysfunction.

General disorders and administrative site conditions:

Frequent: Asthenia.

Less frequent: Chest pain, malaise, peripheral oedema, pyrexia, fatigue.

Investigations:

Less frequent: Increased blood urea, increased blood creatinine, increased blood bilirubin, increased hepatic enzyme, decreased haemoglobin and decreased haematocrit (see section 4.4).

Frequency unknown: Increased blood glucose, increased blood uric acid, electrocardiogram QT prolonged (see sections 4.4 and 4.5).

Injury, poisoning and procedural complications:

Less frequent: Fall.

Cases of Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) have been reported with other ACE-inhibitors. SIADH can be considered as an infrequent 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

Symptoms

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 sodlum levels, low potassium levels) may occur.

Management

The first measures to be taken consist of rapidly eliminating the product(s) ingested by 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 patient 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 (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Perindopril and diuretic.

ATC: C09BA04.

Pharmacological classification: A 7.1.3 Other hypotensives.

ACTI-PREX PLUS is a combination of perindopril tert-butylamine salt an angiotensin-converting enzyme inhibitor (ACE-inhibitor), and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.

Mechanism of action:

ACTI-PREX PLUS produces an added synergy of the antihypertensive effects of the two components.

Perindopril acts through its active metabolite, perindoprilat by inhibiting angiotensin converting enzyme which converts angiotensin I to angiotensin II, a vasoconstricting substance. In addition, the enzyme stimulates the secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides. This results in:

- a reduction in aldosterone secretion.
- an increase in plasma rennin activity, since aldosterone no longer exercises negative feedback.
- a reduction in total peripheral resistance with a preferential action on the vascular bed in muscle and the kidney with no accompanying salt and water retention or reflex tachycardia, with chronic treatment.

The other metabolites of perindopril are inactive.

Indapamide, [N-(3-sulpha oyl-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.

Pharmcodynamic effects

In hypertensive patients regardless of age, ACTI-PREX PLUS exerts a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing. This

antihypertensive effect lasts for 24 hours. The reduction in blood pressure is obtained in less than one month without tachyphylaxis; stopping treatment has no rebound effect. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the products administered alone.

5.2 Pharmacokinetic properties

Absorption

Linked to perindopril

Following oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. Absorption is relatively complete (plasma availability above 75 %). The plasma half-life of perindopril is equal to 1 hour. In terms of trough versus peak blood pressure effect, the trough effect ranges between 75 – 100 % of peak effects.

Linked to indapamide

Indapamide is rapidly and completely absorbed from the digestive tract.

Distribution

Linked to perindopril

Perindopril and perindoprilat both have a low volume of distribution and plasma protein binding is weak but is concentration dependent. Perindoprilat binds to angiotensin converting enzyme at both plasma and tissue levels.

Linked to indapamide

Plasma protein binding is 79 %.

Biotransformation

Linked to perindopril

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat,

perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

Linked to indapamide

The peak plasma level reached in humans is approximately one hour after oral administration of the product.

Elimination

Linked to perindopril

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 halt-life of about 25 hours, resulting in steady state within 4 days.

Linked to indapamide

The elimination half-life is between 14 and 24 hours (average 18 hours).

Repeated administration does not produce accumulation. Elimination is mainly in the urine (70 % of the dose) and faeces (22 %) in the form of inactive metabolites.

Linearity/non-linearity

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Special Patient Populations:

Linked to perindopril

Elderly / Renal Failure / Heart Failure:

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure.

Renal impairment:

Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

In case of dialysis:

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Cirrhosis:

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

Linked to indapamide

Renal insufficiency:

The pharmacokinetics of patients with renal failure is unaffected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrophobic colloidal silica

Lactose monohydrate

Magnesium stearate

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, protected against moisture.

Store in original packaging and keep blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

ACTI-PREX PLUS is packed in a clear PVC film coated with PVDC/Aluminium blister pouch with desiccant.

Blister strips are packed in an outer cardboard box with a leaflet in pack sizes of 30’s, 90’s or 100’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

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Centurion

0157

8. REGISTRATION NUMBER(S)

47/7.1.3/0381

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 February 2022

10. DATE OF REVISION OF THE TEXT