PROFESSIONAL INFORMATION

PEARINDA PLUS 4

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PEARINDA PLUS 4 tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

PEARINDA PLUS 4: Contains sugar (lactose monohydrate 61,53 mg per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated tablet.

PEARINDA PLUS 4: A white capsule shaped tablet with dimensions of 8 mm x 4 mm approximately, bearing a break-line on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PEARINDA PLUS 4 is indicated for the treatment of essential hypertension, in patients that have been stabilised on the individual components at the same dosage ranges and where fixed combination is considered more appropriate than monotherapy.

4.2 Posology and method of administration

Posology

Direct change from monotherapy to PEARINDA PLUS 4 may be considered where clinically

appropriate.

The dosage regimen depends upon the individual requirements of the patient and is at the discretion of the medical doctor.

The recommended dosage is one tablet daily.

Special populations

Renal insufficiency

Treatment with PEARINDA PLUS 4 is contraindicated in severe renal insufficiency (creatinine clearance below 30 mL/min).

It is recommended that treatment should be started with the adequate dosage of the free combination in patients with a creatinine clearance of 30 to 60 mL/minute. No dosage adjustment is necessary in patients with a creatinine clearance greater than 60 mL/minute.

Elderly (see section 4.4)

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

Paediatric population

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

Method of administration

Oral use.

It is recommended that PEARINDA PLUS 4 is taken once daily in the morning before a meal.

Missed dose

Doctors should advise patients who forget to take PEARINDA PLUS 4 to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to

compensate for the missed dose.

4.3 Contraindications

- hypersensitivity to perindopril, indapamide, sulphonamides, any other ACE inhibitor or to any of the ingredients of PEARINDA PLUS 4 (see section 6.1)
- patients with a history of angioedema related to previous ACE inhibitor therapy or angiotensin receptor blockers (ARBs): Patients should never again be given these medicines (see section 4.4)
- hereditary or idiopathic angioedema
- concomitant use of fluoroquinolones with ACE inhibitors/ ARBs, such as PEARINDA PLUS 4, is contraindicated in patients with moderate to severe renal impairment (creatinine clearance <30 mL/min) and in elderly patients
- aortic stenosis
- hypertrophic obstructive cardiomyopathy (HOCM)
- uncompensated cardiac failure
- severe renal function impairment (creatinine clearance below 30 mL/min) or anuria
- bilateral renal stenosis or renal artery stenosis in patients with a single kidney
- concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.4)
- porphyria
- thiazide diuretics, such as PEARINDA PLUS 4, should not be given to patients with Addison's disease
- hypokalaemia
- patients with hepatic cirrhosis, as these patients are more likely to develop hypokalaemia
- severe impairment of liver function or hepatic encephalopathy
- lithium: Concomitant administration with PEARINDA PLUS 4 may lead to a toxic blood concentration of lithium

- concomitant use of PEARINDA PLUS 4 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)
- dialysis patients
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving PEARINDA PLUS 4, the treatment must be stopped promptly and changed to a different class of antihypertensive medicine (see sections 4.3 and 4.6). If a woman is contemplating pregnancy, a different class of antihypertensive medicine should be used (see section 4.6).

Common to perindopril and indapamide

Lithium:

The combination of lithium with the combination of perindopril and indapamide is contraindicated (see sections 4.3 and 4.5).

Linked to perindopril

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 and hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of PEARINDA PLUS 4 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 sections 4.3 and 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, immunosuppressant treatment, 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 treatment. 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:

In those patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney who are treated with ACE inhibitors, the risk of hypotension and renal insufficiency is increased (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, which may be reversible upon discontinuation of treatment even in patients with unilateral renal artery stenosis.

Hypersensitivity/ angioedema:

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been observed rarely in patients treated with ACE inhibitors, including PEARINDA PLUS 4. This may occur at any time during treatment. In these cases, PEARINDA PLUS 4 should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. These patients should never receive any PEARINDA PLUS 4, ACE Inhibitors or angiotensin receptor blockers again (see section 4.3).

ACE inhibitors, including PEARINDA PLUS 4, cause a higher rate of angioedema in patients of black ethnicity than in non-black patients.

Signs of facial or extremity swelling or difficulty in swallowing or breathing, require immediate medical attention, because of the risk of angioedema. PEARINDA PLUS 4 should be discontinued.

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 PEARINDA PLUS 4 (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) 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 treatment. If treatment with sacubitril/valsartan is stopped, perindopril treatment 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 neutral endopeptidase (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 ARBs:

Concomitant use of fluoroquinolones and ACE inhibitors/ARBs, such as PEARINDA PLUS 4, may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and in elderly patients (see section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors / ARBs, whether used separately and/or concomitantly.

Anaphylactoid reactions during desensitisation:

Anaphylactoid reactions have occurred in patients using ACE inhibitors, including PEARINDA PLUS 4, during desensitising protocols involving for example, hymenoptera venom. PEARINDA PLUS 4 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 PEARINDA PLUS 4 for at least 24 hours before treatment in patients who require both

ACE inhibitors and desensitisation.

Anaphylactoid reactions during low density lipoprotein (LDL) apheresis:

Life threatening anaphylactoid reactions have been reported in patients exposed to low density lipoprotein apheresis with dextran sulphate absorption. PEARINDA PLUS 4 should be avoided in such patients. Anaphylactoid reactions can however, be avoided by withdrawing treatment of PEARINDA PLUS 4 at least 24 hours before treatment in those patients requiring both ACE inhibitor and LDL apheresis treatment.

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients exposed to high-flux membrane dialysis (e.g. AN69®) on ACE inhibitor treatment. 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 PEARINDA PLUS 4 is not recommended.

Linked to indapamide

Hepatic encephalopathy:

Hepatic encephalopathy may be precipitated by thiazide and thiazide related diuretics in patients with severe hepatic impairment. Administration of PEARINDA PLUS 4 should be stopped immediately if this happens.

Photosensitivity:

Photosensitivity reactions have been reported with thiazides and related thiazide diuretics (see

section 4.8). If, during treatment, photosensitivity reactions occur, treatment should be stopped. If a re-administration of the diuretic is deemed necessary, patients should be informed to protect exposed areas of skin to both the sun and to artificial UVA.

Linked to PEARINDA PLUS 4

Renal insufficiency:

In cases of severe renal insufficiency (creatinine clearance < 30 mL/min), treatment is contraindicated (see section 4.3).

Treatment should be stopped and possibly restarted with one constituent only in patients without pre-existing apparent renal lesions in whom renal blood flow tests show functional renal insufficiency.

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.

In those patients with bilateral renal artery stenosis or a single functioning kidney, PERAINDA PLUS 4 is contraindicated (see section 4.3).

Myocardial infarction:

In acute myocardial infarction, treatment with PEARINDA PLUS 4 should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 micromol/L or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 micromol/L or doubling of the pre-treatment value), then PEARINDA PLUS 4 may need to be withdrawn (see section 4.3).

In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.

Hypotension in acute myocardial infarction - treatment with PEARINDA PLUS 4 must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 100 mm Hg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. Maintenance doses should be reduced if systolic blood pressure is 100 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg or more than 1 hour), then PEARINDA PLUS 4 should be withdrawn.

Hypotension and water and electrolyte depletion:

Patients at a high risk of symptomatic hypotension e.g. patients with salt or volume depletion (in particular in patients with renal artery stenosis) with or without hyponatraemia should have these conditions corrected before therapy with PEARINDA PLUS 4. Systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur during episodes of diarrhoea and/or vomiting. Regular monitoring of plasma electrolytes is required after initiating and during therapy. If hypotension occurs, the patient should be placed in the supine position and if necessary receive an intravenous infusion of 0,9 % 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 with only one of the constituents.

Potassium levels:

The onset of hypokalaemia is not prevented by the combination of perindopril and indapamide, particularly in patients with renal failure and diabetic patients. Potassium levels should be monitored regularly.

Cerebrovascular disease or ischaemic heart disease:

Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular accidents.

Blood urea and serum creatinine:

Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when PEARINDA PLUS 4 has been given concomitantly with a diuretic. Dosage reduction or discontinuation of PEARINDA PLUS 4 or the diuretic may be required.

Information on excipients of PEARINDA PLUS 4

PEARINDA PLUS 4 contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Linked to perindopril

Cough:

A dry persistent cough, that disappears on discontinuation of treatment, has been associated with ACE inhibitors. An iatrogenic aetiology should be considered in the event of this symptom. If an ACE inhibitor is the preferred therapy, 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.):

Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or

vomiting) – although it may occur in normo-volemic patients, hypotension is more likely in volume depleted patients. A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of PEARINDA PLUS 4 induced renal failure, especially in those with congestive heart failure, in patients whose blood pressure was initially low, in cases of renal artery stenosis 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:

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

Patients with known atherosclerosis:

Myocardial infarction and cerebrovascular accidents may be due to severe falls in blood pressure in high-risk patients e.g. those with atherosclerosis, ischaemic heart disease or cerebrovascular disease. Treatment should be started at a low dose or 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:

Severe cardiac insufficiency (grade IV) or patients with insulin dependent diabetes mellitus (tendency to hypokalaemia) – start treatment with a low dose or one constituent only under strict medical supervision. Treatment with beta blockers should not be stopped in hypertensive patients with coronary insufficiency, the ACE inhibitor should be added to the beta blocker.

Patients with diabetes:

Increased risk of hyperkalaemia, as well as hypoglycaemia may occur especially in insulin-dependent diabetes mellitus. Treatment should therefore be started under medical supervision and with a reduced initial dose.

It is important to monitor blood glucose levels in diabetic patients previously treated with oral antidiabetic medication or insulin especially when potassium levels are low, 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 patients of black ethnicity than in non-black patients, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Surgery/anaesthesia:

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, PEARINDA PLUS 4 may block angiotensin II formation secondary to complementary renin release.

If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. However, it is recommended that treatment with perindopril be discontinued one day before surgery where possible.

Hypertrophic cardiomyopathy:

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

Hepatic failure:

A syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death has been associated with PEARINDA PLUS 4. The mechanism of this syndrome is not understood. Patients receiving PEARINDA PLUS 4 who develop jaundice or marked elevations of hepatic enzymes should discontinue treatment and receive appropriate medical follow up (see section 4.8.)

Hyperkalaemia/hypokalaemia:

PEARINDA PLUS 4 may cause an increase or decrease in serum potassium levels. The following patients are at risk for changes in serum potassium levels: those with uncontrolled diabetes mellitus, renal insufficiency, malnourishment, coronary problems or heart failure, cirrhotic patients with oedema or ascites, the elderly (> 70 years), those with inter-current events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and those using concomitant potassium supplements, potassium-sparing diuretics such as spironolactone, triamterene and amiloride (may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysrhythmias and cardiac arrest), or potassium containing salt substitutes; or those patients on other medication associated with changes of serum potassium levels (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). Regular monitoring of serum potassium is recommended, if concomitant use of the abovementioned agents is deemed appropriate (see section 4.5).

Linked to indapamide

Water and electrolyte balance:

Indapamide may cause electrolyte imbalances and a reduction in sodium levels which may have serious consequences. Sodium levels should be tested before initiation of treatment and then at regular intervals during treatment.

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:

A major risk of thiazide diuretics and thiazide related diuretics is

potassium depletion with hypokalaemia. The risk of onset of lowered potassium levels (< 3,4 mmol/L) should be prevented in some high risk populations such as malnourished subjects and/or the elderly (whether or not they are taking multiple medications), coronary patients and patients with heart failure, and cirrhotic patients with ascites and oedema. 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 required. 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:

The urinary excretion of calcium may be reduced by thiazide diuretics and thiazide related diuretics, and this may lead to a mild and transient increase in plasma calcium levels. In the case of a marked increase of calcium levels, treatment should be stopped before investigation of the parathyroid function to prevent undiagnosed hyperparathyroidism.

Blood glucose:

It is important to monitor blood glucose levels in diabetic patients, especially when potassium levels are low.

Uric acid:

In hyperuricaemic patients there may be an increased tendency of gout attacks.

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 micromol/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) x body weight/ 0,814 x plasma creatinine Level

with: age expressed in years

body weight in kg

plasma creatinine level in micromol/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 note that this product contains indapamide, which may give a positive reaction in drug tests.

Paediatric population

Safety and efficacy in children have not been established.

4.5 Interaction with other medicines and other forms of interaction

Linked to PEARINDA PLUS 4

***Concomitant use contraindicated*:**

Concomitant treatment with lithium is contraindicated as toxic blood concentrations of lithium may result (see section 4.3).

***Concomitant use which requires special care*:**

Baclofen:

The antihypertensive effect may be potentiated. Monitoring of blood pressure with adaption of antihypertensive dose where necessary is recommended.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (systemic route) and high dose salicylates (including aspirin ≥ 3 g/day):

Simultaneous administration of ACE inhibitors with nonsteroidal 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 inhibitor and NSAIDs may lead to acute renal insufficiency, including acute renal failure and an increase in serum potassium, especially in dehydrated patients (reduction in glomerular filtration rate) and in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly.

Patients should be well hydrated and renal function should be monitored at the start of concomitant treatment and periodically thereafter.

***Concomitant use requiring care*:**

Tricyclic antidepressants, neuroleptics:

Increased antihypertensive effect and increased risk of orthostatic hypotension.

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).

Hyperkalaemia inducing medicines:

Some medicines or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium supplements or potassium sparing diuretics such as spironolactone, triamterene or amiloride, ACE inhibitors, angiotensin-II receptor antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim. Concurrent administration 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-inhibitors may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril treatment. Perindopril treatment 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 ARBs:

Concomitant use of fluoroquinolones and ACE inhibitors/ ARBs, such as PEARINDA PLUS 4, may

precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above the 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 treatment 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 PEARINDA PLUS 4, 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 under section 4.5 *Concomitant use which requires special care*.

***Concomitant use which requires special care*:**

Antidiabetic agents (insulin, hypoglycaemic sulphonamides):

The hypoglycaemic effects may be increased 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 treatment 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 treatment with low and progressive doses of perindopril. Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

In arterial hypertension:

When prior diuretic treatment may 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 thereafter be 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 treatment.

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 treatment, 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 PEARINDA PLUS 4. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

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

Concomitant administration may lead to an increased risk for leucopenia (see section 4.4).

Anaesthetic agents:

The hypotensive effects of certain anaesthetic agents may be enhanced (see section 4.4).

Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin):

Increased risk of angioedema, 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 treatment with injectable gold (auranofin) and concomitant ACE-inhibitor treatment including perindopril.

Linked to indapamide

Concomitant use that requires special care

Antidysrhythmic medicines, 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 antidysrhythmic agents (quinidine, hydroquinidine, disopyramide); class III antidysrhythmic 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 mizolastine, moxifloxacin, pentamidine, pimozide, sparfloxacin, IV erythromycin, halofantrine, vincamine, methadone, astemizole and 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 β_2-agonists:

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.

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 not use metformin when plasma creatinine levels exceed 15 mg/L (135 micromol/L) in men and 12 mg/L (110 micromol) in women.

Iodinated contrast media:

There is an increased risk of acute renal insufficiency, in cases of dehydration caused by indapamide, 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 or tacrolimus:

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

Indomethacin and nonsteroidal anti-inflammatory medicines (NSAID's):

Reduce the antihypertensive effects of PEARINDA PLUS 4. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with PEARINDA PLUS 4.

Cardiac glycosides:

The toxic effects of cardiac glycosides are favoured by low potassium levels.

Anticoagulants, coumarin- or indandione-derivative:

Effects may be decreased when used concurrently with indapamide. In addition, diuretic-induced improvement in hepatic congestion may lead to improved hepatic function resulting in increased pro-coagulant factor synthesis, dosage adjustments may be necessary.

Non-depolarising neuromuscular blocking agents:

Indapamide may induce hypokalaemia, which may enhance the blockade of non-depolarising neuromuscular blocking agents. Serum potassium should be determined before administration of non-depolarising neuromuscular blocking agents.

Sympathomimetics:

The antihypertensive effects of indapamide may be reduced.

Corticosteroids, tetracosactide (systemic route):

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

4.6 Fertility, pregnancy and lactation

Pregnancy

PEARINDA PLUS 4 is contraindicated during pregnancy.

Pregnant women should be informed of the potential hazards to the foetus and must not take PEARINDA PLUS 4 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 PEARINDA PLUS 4 should be stopped and if appropriate, alternative treatment 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.

PEARINDA PLUS 4 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).

Breastfeeding

PEARINDA PLUS 4 is contraindicated during breastfeeding (see section 4.3).

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 breastfeeding 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 breastfeeding, 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

Caution is advised when driving or performing tasks requiring alertness because of possible dizziness related to a reduction in blood pressure.

4.8 Undesirable effects

Summary of the 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 perindopril/indapamide combination tablet experienced 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 summary of adverse reactions PEARINDA PLUS 4

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Decreases in white blood cell count, haemoglobin and haematocrit, bone marrow depression, anaemia, thrombocytopenia, agranulocytosis, haemolytic anaemia

Immune system disorders	Less frequent	Hypersensitivity/angioedema reactions, angioedema of the face, extremities, lips, tongue, glottis and/or larynx, which may be fatal, intestinal angioedema. A symptom complex has been reported which may include: fever, vasculitis, myalgia, arthritis/ arthralgia, a positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis
Metabolism and nutrition disorders	Frequent Less frequent	Hypokalaemia – perindopril inhibits the renin-angiotensin-aldosterone axis and reduces the potassium loss induced by indapamide Hyperkalaemia, hyponatraemia, increases in blood urea and blood glucose, increases in serum creatinine, raised plasma calcium levels, hypochloraemic alkalosis, indapamide may precipitate secondary gout
Nervous system disorders	Frequent Less frequent	Vertigo, fatigue Dizziness, headache, paraesthesia, mood alterations, sleep disturbances, asthenia and mental confusion
Eye disorders	Less frequent	Vision disturbance
Cardiac disorders	Frequent Less frequent	Orthostatic effects, including hypotension Myocardial infarction, cerebrovascular accident, palpitations, tachycardia, chest pain

Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Cough Bronchospasm, rhinitis, sinusitis
Gastrointestinal disorders	Frequent Less frequent	Diarrhoea, nausea, abdominal pain, indigestion, vomiting, taste disturbances, dry mouth, constipation, epigastric pain, anorexia Pancreatitis
Hepatobiliary disorders	Less frequent	Jaundice, increases in liver enzymes, increases in serum bilirubin, hepatitis (hepatocellular or cholestatic)
Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus Urticaria, diaphoresis, alopecia, psoriasis, severe skin disorders including pemphigus, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. skin rash, photosensitivity or other dermatological manifestations may occur. Hypersensitivity reactions, mainly dermatological in subjects with a predisposition to allergic and asthmatic reactions. Maculopapular eruptions, purpura, possible aggravation of pre-existing acute disseminated lupus erythematosus
Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscle cramps
Renal and urinary disorders	Less frequent	Uraemia, oliguria, anuria, renal dysfunction, acute renal failure

Reproductive system and breast disorders	Less frequent	Impotence

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

Tabulated summary of adverse reactions PERINDOPRIL

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Rhinitis
Blood and lymphatic system disorders	Less frequent	Eosinophilia*, agranulocytosis, aplastic anaemia, pancytopenia, leukopenia, neutropenia, haemolytic anaemia, thrombocytopenia
Metabolism and nutrition disorders	Less frequent	Hypoglycaemia*, hyperkalaemia* (reversible on discontinuation), hyponatraemia*
Psychiatric disorders	Less frequent	Mood altered, sleep disorder, confusion
Nervous system disorders	Frequent Less frequent	Dizziness, headache, paraesthesia, dysgeusia Somnolence*, syncope*, stroke
Eye disorders	Frequent	Visual impairment
Ear and labyrinth disorders	Frequent	Vertigo, tinnitus
Cardiac disorders	Less frequent	Palpitations*, tachycardia*, angina pectoris, dysrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation), myocardial infarction

Vascular disorders	Frequent Less frequent Frequency unknown	Hypotension Vasculitis* Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Cough, dyspnoea Bronchospasm, eosinophilic pneumonia
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting Dry mouth, pancreatitis
Hepatobiliary disorders	Less frequent	Hepatitis
Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus, rash Urticaria, angioedema, hyperhidrosis, photosensitivity reaction*, pemphigoid*, psoriasis aggravation*, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Muscle cramps Arthralgia*, myalgia*
Renal and urinary disorders	Less frequent	Renal insufficiency, renal failure acute
Reproductive system and breast disorders	Less frequent	Erectile dysfunction
General disorders and administrative site conditions	Frequent Less frequent	Asthenia Chest pain*, malaise*, peripheral oedema*, pyrexia*
Investigations	Less frequent	Blood urea increased*, blood creatinine increased*, blood bilirubin increased, hepatic enzyme increased, haemoglobin and haematocrit decreased

Injury and poisoning	Less frequent	Fall*

Tabulated summary of adverse reactions INDAPAMIDE

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, aplastic anaemia, leukopenia, haemolytic anaemia, thrombocytopenia
Immune system disorders	Frequent	Hypersensitivity (reactions mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions)
Metabolism and nutrition disorders	Less frequent Frequency unknown	Hyponatraemia, hypercalcaemia, Potassium depletion with hypokalaemia
Nervous system disorders	Less frequent Frequency unknown	Headache, paraesthesia Syncope, possibility of onset of hepatic encephalopathy in case of hepatic insufficiency
Eye disorders	Frequency unknown	Visual impairment, myopia, blurred vision
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent Frequency unknown	Dysrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation) *Torsade de pointes* (potentially fatal)
Vascular disorders	Less frequent	Hypotension (and effects related to hypotension)
Gastrointestinal disorders	Less frequent	Constipation, nausea, vomiting, dry mouth, pancreatitis
Hepatobiliary disorders	Less frequent Frequency unknown	Hepatic function abnormal Hepatitis

Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Rash maculopapular Urticaria, angioedema, purpura, toxic epidermal necrolysis, Stevens Johnson Syndrome Photosensitivity reaction
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Possible worsening of pre existing acute disseminated lupus erythematosus
Renal and urinary disorders	Less frequent	Renal failure acute
General disorders and administrative site conditions	Less frequent	Fatigue
Investigations	Frequency unknown	Hepatic enzyme increased, blood glucose increased, blood uric acid increased, electrocardiogram QT prolonged

* 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 treatment 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 online service for adverse drug reaction reporting by using either of the following links: https://www.sahpra.org.za/Publications/Index/8 or http://www.sahpra.org.za/ document/adverse-drug-reactions-and-quality-problem-reporting-form/.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms

Severe hypotension (sometimes associated with cramps, nausea, vomiting, sleepiness, dizziness, mental confusion), electrolyte disturbances (low sodium and potassium levels) and renal failure (oliguria which may progress to anuria due to hypovolaemia).

Management of overdose

Treatment is symptomatic and supportive. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume expansion to correct hypotension and treating dehydration and electrolyte imbalances.

Perindopril and perindoprilat are removable by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: perindopril and diuretics

ATC code: C09BA04

Pharmacological classification: A 7.1.3 Other hypotensives.

Mechanism of action

PEARINDA PLUS 4 is a combination of perindopril tert-butylamine salt, and indapamide, a chlorosulphamoyl diuretic. Perindopril inhibits angiotensin I-converting enzyme (ACE) activity through its active metabolite, perindoprilat. It is a specific non-sulphydryl competitive ACE inhibitor. It inhibits the conversion of the relatively inactive angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels

results in a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium. It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

Indapamide, [N-(3-sulphamoyl-4-chlorobenzamido) 2-methyl indoline] is an indole derivative of chlorosulphonamide with antihypertensive action. It has 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 PGE2. 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.

5.2 Pharmacokinetic properties

Absorption

Perindopril is well absorbed after oral doses with a bioavailability of about 65 to 75 % and reaching peak concentration within 1 hour. Peak plasma concentrations of perindoprilat are achieved within 3 to 4 hours of an oral dose of perindopril. The time to peak effect is 3 to 7 hours. The presence of food does not affect the rate or extent of absorption of perindopril, but it is reported to reduce the conversion of perindopril to perindoprilat.

Indapamide is rapidly and completely absorbed from the gastrointestinal tract. Peak plasma concentrations are achieved within about 2 hours.

Distribution

Perindopril and perindoprilat have a low volume of distribution. The plasma protein binding of perindoprilat is weak (about 10 to 20 %). Perindoprilat binds to angiotensin converting enzyme at both plasma and tissue levels. Indapamide is strongly bound to plasma proteins.

Biotransformation

Perindopril is extensively metabolised in the liver to perindoprilat and inactive metabolites, including

glucuronides.

Indapamide is extensively metabolised in the liver.

Elimination

Perindopril is mainly excreted in the urine as unchanged perindopril (the elimination half-life is about 1 hour), as perindoprilat, and as other metabolites. The remainder is excreted in the faeces. Perindoprilat has a biphasic elimination with a distribution half-life of about 5 hours and an elimination half-life of 25 to 30 hours or longer. The latter half-life probably represents strong binding to angiotensin-converting enzyme. Perindoprilat excretion is decreased in renal impairment. Both perindopril and perindoprilat are removed by dialysis.

Indapamide elimination is biphasic with a half-life in whole blood of about 14 hours. About 60 to 70 % of the dose is excreted in the urine, about 5 to 7 % is excreted unchanged. About 16 to 23 % of the dose is excreted in the faeces. Indapamide is not removed by haemodialysis, but it doesn't accumulate in patients with renal impairment.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Silica colloidal anhydrous.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

PEARINDA PLUS 4: The tablets are available in PA/ALU/PVC/ALU blister packs of 30 tablets in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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