PROFESSIONAL INFORMATION (APPROVED)

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PEARINDA PLUS 8, tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg perindopril *tert*-butylamine and 2,5 mg indapamide.

Contains sugar (lactose monohydrate 123,06 mg per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to almost white, circular tablets, bearing a break-line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PEARINDA PLUS 8 is indicated for the treatment of essential hypertension, in patients where blood pressure is not adequately controlled and where fixed combination is considered more appropriate than monotherapy.

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4.2 Posology and method of administration

Posology

One PEARINDA PLUS 8 tablet per day as a single dose, preferably to be taken in the morning, before a meal.

Special populations

Elderly:

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

Patients with renal impairment:

In cases of severe renal impairment (creatinine clearance below 30 mL/min), treatment is contraindicated (see section 4.3). 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. Usual medical follow-up will include frequent monitoring of creatinine and potassium.

Patients with hepatic impairment:

In severe hepatic impairment, treatment is contraindicated (see section 4.3). In patients with moderate hepatic impairment, no dose modification is required.

Paediatric population

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PEARINDA PLUS 8 should not be administered to children and adolescents as the efficacy and safety of perindopril (as contained in PEARINDA PLUS 8), either alone or in combination in this patient population, have not been established.

Missed dose

Doctors should advise patients who forget to take PEARINDA PLUS 8 to take the next dose at the normal time. Patients should not take a double dose to compensate for the missed dose.

Method of administration

For oral use

PEARINDA PLUS 8 should be taken in the morning, before a meal.

4.3 Contraindications

Linked to perindopril:

- hypersensitivity to perindopril tert-butylamine, or to any other ACE inhibitor
- patients with a history of angioedema related to previous ACE inhibitor therapy, angiotensin receptor blockers (ARBs) or renin inhibitors: these patients should never again be given these medicines (see section 4.4)
- hereditary or idiopathic angioedema
- concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers is contraindicated in patients with moderate to severe renal function impairment (creatinine

clearance less than 30 mL/min) and in the elderly

- hypertrophic obstructive cardiomyopathy (HOCM)
- severe renal impairment (creatinine clearance less than 30 mL/min), or anuria
- 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, amiloride), potassium supplements or potassium-containing salt substitutes (see section 4.4)
- porphyria
- lithium: concomitant administration with PEARINDA PLUS 8 may lead to toxic blood concentrations of lithium (see section 4.5)
- the concomitant use of PEARINDA PLUS 8 with aliskiren-containing products in patients with diabetes or renal impairment (GFR < 60 mL/min/1,73 m^2) is contraindicated (see section 4.4)
- 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)
- pregnancy and lactation.

Linked to indapamide:

- hypersensitivity to indapamide or any other sulphonamides
- severe renal impairment (creatinine clearance below 30 mL/min)

- hepatic encephalopathy
- severe hepatic impairment
- hypokalaemia
- concomitant use with non-antidysrhythmic medicines causing *torsades de pointes* (see section 4.5)
- lactation.

Linked to PEARINDA PLUS 8:

- hypersensitivity to any of the excipients listed in section 6.1
- dialysis patients
- patients with untreated decompensated heart failure
- PEARINDA PLUS 8, should not be given to patients with Addison's disease.

4.4 Special warnings and precautions for use

Common to perindopril and indapamide:

Lithium

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

Linked to perindopril:

Should a woman become pregnant while receiving PEARINDA PLUS 8, the treatment should be stopped promptly and switched to a

different class of antihypertensive medicine (see sections 4.3 and 4.6).

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

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers (ARBs) or renin inhibitors such as aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of PEARINDA PLUS 8 and aliskiren is therefore contraindicated (see section 4.3). 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 PEARINDA PLUS 8 and potassium-sparing diuretics (such as spironolactone, triamterene and amiloride), potassium supplements or potassium-containing salt substitutes may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysrhythmias, and cardiac arrest (see sections 4.3 and 4.5) and is therefore contraindicated.

Neutropenia/agranulocytosis/thrombocytopenia/anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors such as in PEARINDA PLUS 8.

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PEARINDA PLUS 8 may cause bone marrow depression, and therefore an increased risk of agranulocytosis and neutropenia.

In patients with normal renal function and no other complicating factors, neutropenia may occur. PEARINDA PLUS 8 should be used with caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which did not respond to intensive antibiotic therapy. If PEARINDA PLUS 8 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 4.8).

Autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma, increase the risk for development of neutropenia or agranulocytosis.

Renovascular hypertension

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

Hypersensitivity/angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients

treated with angiotensin converting enzyme inhibitors, including perindopril (see section 4.8). This may occur at any time during treatment. In such cases PEARINDA PLUS 8 should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms (see section 4.3).

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 a subcutaneous injection of epinephrine (adrenaline) at 1:1000 (0,3 mL to 0,5 mL) 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 8, ACE inhibitors or angiotensin receptor blockers again (see section 4.3).

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

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving PEARINDA PLUS 8 (see section 4.3). Intestinal angioedema has been reported in patients treated with ACE inhibitors such as PEARINDA PLUS 8. 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 at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be

included in the differential diagnosis of patients on PEARINDA PLUS 8 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).

Sacubitril/valsartan

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 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.

Anaphylactic reactions during low-density lipoproteins (LDL) apheresis

Patients receiving PEARINDA PLUS 8 during low density lipoprotein (LDL)-apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. PEARINDA PLUS 8 should be

avoided in such patients. These reactions were avoided by temporarily withholding ACE inhibitors, such as PEARINDA PLUS 8 therapy, for at least 24 hours prior to each apheresis for patients who require both ACE inhibitors and LDL apheresis.

Anaphylactic reactions during desensitisation

Life-threatening anaphylactoid reactions have occurred in patients using ACE inhibitors, including PEARINDA PLUS 8, during desensitising protocols involving, for example, hymenoptera (bees, wasps) venom. PEARINDA PLUS 8 should be used with caution in allergic patients treated with desensitisation and avoided in those undergoing venom immunotherapy. These reactions were, however, avoided when the ACE inhibitors were temporarily withheld for at least 24 hours before treatment in patients who require both ACE-inhibitors and desensitisation.

Haemodialysis patients

Anaphylactic reactions have been reported in patients dialysed with high flux membranes (e.g., AN 69®), and treated concomitantly with an ACE inhibitor, such as in PEARINDA PLUS 8. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive medicine.

Anaemia has been observed in patients who have had a kidney transplant or have been undergoing dialysis. The reduction in haemoglobin levels is more apparent if initial values were high. This reduction is slight, occurs within 1 to 6 months, and then remains stable. It is reversible when the treatment is stopped. Treatment can be confirmed with regular haematological testing.

Primary aldosteronism

Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive medication acting through inhibition of the renin-angiotensin system. Therefore, the use PEARINDA PLUS 8 is not recommended.

Linked to indapamide:

Hepatic encephalopathy

When liver function is impaired, thiazide diuretics and thiazide-related diuretics such as indapamide (contained in PEARINDA PLUS 8) may cause hepatic encephalopathy. Administration of PEARINDA PLUS 8 should be stopped immediately if this occurs.

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazides and related thiazide diuretics such as indapamide (contained in PEARINDA PLUS 8), (see section 4.8). If a photosensitivity reaction occurs during treatment, it is recommended treatment be stopped. If a re-administration of the diuretic is necessary, it is recommended that areas of skin exposed to sun or artificial UVA, be protected.

Special precautions linked to perindopril and indapamide combination:

Renal impairment

In certain hypertensive 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 active ingredient only.

In these patients, usual medical follow up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis (see section 4.3). PEARINDA PLUS 8 should not be used in case of bilateral renal artery stenosis or a single functioning kidney (see section 4.3).

Hypotension and water 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 inter-current 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 with only one of the constituents.

Potassium levels

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

Special precautions linked to perindopril:

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/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/angiotensin receptor blockers whether used separately or concomitantly.

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 PEARINDA PLUS 8 is still preferred, and if the patient can tolerate the cough, continuation of treatment may be considered.

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 of this system by PEARINDA PLUS 8 may therefore cause, particularly at 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, and with a variable time to onset. In such cases, the treatment should then be initiated with only one of the constituents and increased progressively.

Elderly

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

Arthrosclerosis

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

Renovascular hypertension

The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when 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. PEARINDA PLUS 8 is contraindicated in patients with renal artery stenosis.

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 with PEARINDA PLUS 8 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, an ACE inhibitor, such as PEARINDA PLUS 8, should be added to the beta-blocker.

Cerebrovascular disease or ischaemic heart disease

Reduction in blood pressure could aggravate cerebrovascular disease (such as atherosclerosis) or ischaemic heart disease and may result in myocardial infarction and cerebrovascular accidents.

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 medicines or insulin, namely during the first month of treatment with PEARINDA PLUS 8 (see section 4.5).

Ethnic differences

PEARINDA PLUS 8 may be less effective in lowering blood pressure in black people than in other ethnic groups, possibly because of a higher prevalence of low-renin levels in the black hypertensive population.

Surgery/anaesthesia

In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, PEARINDA PLUS 8 may block angiotensin II formation secondary to compensatory renin release. The treatment with ACE-Inhibitors should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Aortic or mitral valve stenosis/hypertrophic cardiomyopathy

PEARINDA PLUS 8 should not be used in patients with mitral valve stenosis and an obstruction in the outflow tract of the left ventricle, such as aortic stenosis or hypertrophic cardiomyopathy. PEARINDA PLUS 8 is contraindicated in aortic stenosis (see section 4.3).

Hepatic failure

ACE inhibitors, such as in PEARINDA PLUS 8, 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 PEARINDA PLUS 8 who develop jaundice or marked elevations of hepatic enzymes should discontinue PEARINDA PLUS 8 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. Patients at risk for the development of hyperkalaemia include those with uncontrolled diabetes mellitus, worsening of renal insufficiency, age (> 70 years), intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and using potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, amiloride), potassium supplements, or potassium-containing salt substitutes concomitantly; 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 NSAIDs, 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 and therefore concomitant use with any of the above-mentioned medicines is contraindicated.

Special precautions linked to indapamide:

Water and electrolyte balance

Indapamide can cause electrolyte imbalances.

Sodium levels

Sodium levels should be tested before treatment is started, then at regular intervals. Indapamide can cause a reduction in sodium levels, which may have serious consequences. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing

should be more frequent in elderly and cirrhotic patients (see section 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 such as in PEARINDA PLUS 8. The risk of onset of lowered potassium levels (< 3,4 mmol/L) should be prevented in high-risk populations such as elderly and/or malnourished patients, whether or not they are taking multiple medicines, 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 cardiac rhythm disorders.

Patients 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 cardiac rhythm disorders, particularly *torsade 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 levels of potassium are detected, correction is required.

Calcium levels

Thiazide-related diuretics, such as in PEARINDA PLUS 8, 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.

Magnesium levels

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8).

Blood glucose

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

Uric acid

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 slightly impaired (creatinine levels lower than approximately 25 mg/L, i.e., 220 mmol/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 Cockcroft formula:

Cl_{cr} (mL/min) = (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 impairment.

Athletes

Athletes should note that PEARINDA PLUS 8 contains indapamide which may cause a positive reaction in doping tests.

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.

Excipients

PEARINDA PLUS 8 contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take PEARINDA PLUS 8.

Paediatric population

The safety and efficacy of perindopril (as contained in PEARINDA PLUS 8) in children, alone or in combination have not been established.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of PEARINDA PLUS 8 is contraindicated:

Linked to perindopril:

Fluoroquinolones

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

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. The concomitant use of PEARINDA PLUS 8 with lithium is contraindicated (see section 4.3).

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Aliskiren

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

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).

Concomitant use not recommended:

Linked to perindopril:

Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker

In patients with established atherosclerotic disease, heart failure, or with diabetes with end organ

damage, concomitant therapy with an ACE inhibitor and 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 may be at increased risk for hyperkalaemia (see section 4.4).

Concomitant use which requires special care:

Linked to the combination of perindopril and indapamide:

Baclofen

The antihypertensive effect may be potentiated. Monitor blood pressure and adapt antihypertensive dose if necessary.

Linked to perindopril:

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 and trimethoprim (see section 4.3).

The combination of these medicines increases the risk of hyperkalaemia.

Non-steroidal anti-inflammatory medicines (NSAIDs) (including aspirin ≥ 3 g/day)

Non-steroidal anti-inflammatory medicines (including acetylsalicylic acid at high doses): When ACE inhibitors (as in PEARINDA PLUS 8) are administered simultaneously with NSAIDs (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.

Antidiabetic medicines (insulin, oral hypoglycaemic medicines)

The use of ACE inhibitors (such as PEARINDA PLUS 8) and anti-diabetic medicines (insulins, hypoglycaemic medicines) may cause an increased blood-glucose lowering effect with a risk of hypoglycaemia. This appears to be more likely to occur during the first weeks of treatment and in patients with renal impairment.

Non potassium-sparing diuretics

Patients taking diuretics, as well as 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, or by increasing volume or salt intake prior to the initiation of treatment. In arterial hypertension, where previous diuretic treatment has caused salt/volume depletion, the diuretic must be discontinued prior to initiation of treatment with the ACE inhibitor. In diuretic-treated congestive heart failure, an ACE-inhibitor should be initiated at a very low dose, possibly after reducing the dose 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:

Concomitant use of potassium-sparing diuretics in patients with class II-IV heart failure (NYHA) with ejection fraction < 40 %, and who have previously been treated with ACE inhibitors and loop diuretics have a high risk of hyperkalaemia, which may be fatal. Before initiating the combination, the absence of hyperkalaemia and renal impairment needs to be confirmed.

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

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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).

Linked to indapamide:

Torsades de pointes inducing medicines

Due to the risk of hypokalaemia, indapamide (as in PEARINDA PLUS 8), should be administered with caution when associated with medicines known to induce *torsade 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 medicines such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, astemizole, terfenadine and methadone. Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.

Other potassium-lowering medicines causing hypokalaemia: Amphotericin B (IV), gluco- and

mineralo-corticoids (systemic route), tetracosactide, stimulant laxatives

Increased risk of hypokalaemia (additive effect). Potassium levels should be monitored, and corrected, if necessary, particular consideration is required in patients treated with cardiac glycosides. Non stimulant laxatives should be used.

Digoxin

Low potassium levels and/or hypomagnesaemia favour the toxic effects of digoxin. Potassium levels, magnesium levels and EGC should be monitored, and treatment reconsidered if necessary.

Allopurinol

Concomitant treatment with indapamide (as in PEARINDA PLUS 8) may increase the incidence of hypersensitivity reactions to allopurinol.

Concomitant use which requires some care:

Linked to the combination of perindopril and indapamide:

Imipramine-like antidepressants (tricyclics), neuroleptics

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

Linked to perindopril:

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

Clinical trial data have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is

associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see sections 4.3 and 4.4).

Antihypertensive medicines and vasodilators

Concomitant use of these medicines may increase the hypotensive effects of perindopril (as in PEARINDA PLUS 8). 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 use with ACE inhibitors, as in PEARINDA PLUS 8 may lead to increased risk for leucopenia.

Anaesthetic medicines

ACE inhibitors may enhance the hypotensive effects of certain anaesthetic medicines.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypertension when initiating therapy with PEARINDA PLUS 8.

Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin)

There is an increased risk of angioedema, due to dipeptidyl peptidase IV (DPP-IV) decreased

activity by the gliptin, in patients on treatment with gliptins and an ACE inhibitor, as in PEARINDA PLUS 8.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypertension) have been reported rarely in patients on therapy with injectable gold (auranofin) and concomitant ACE inhibitor therapy including perindopril (as in PEARINDA PLUS 8).

Linked to indapamide:

Corticosteroids, tetracosactide

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

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 135 micromol/L (15 mg/L) in men and 110 micromol/L (12 mg/L) in women.

Iodinated contrast media

In cases of dehydration caused by diuretics, 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 medicine is administered.

Calcium (salts)

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

Ciclosporin

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

The use of PEARINDA PLUS 8 is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take PEARINDA PLUS 8 during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with PEARINDA PLUS 8 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.

PEARINDA PLUS 8 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 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 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.

Breastfeeding

The use of PEARINDA PLUS 8 is contraindicated during breastfeeding (see section 4.3).

It is unknown whether perindopril passes into breastmilk, therefore perindopril is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

There is insufficient information on the excretion of indapamide/metabolites in human breast milk. Indapamide is closely related to thiazide diuretics which have been associated with a decrease or suppression of milk lactation during breastfeeding. Hypersensitivity to sulphonamide-derived medicines and hypokalaemia might occur. Indapamide is contraindicated during breastfeeding.

Fertility

Reproductive toxicity studies showed no effect on fertility in female and male rats. No effects on human fertility are anticipated.

4.7 Effects on ability to drive and use machines

Perindopril and indapamide individually, or in combination do not affect alertness but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medicine.

PEARINDA PLUS 8 can cause side effects such as dizziness, visual disturbances and visual impairment.

Caution is advised when driving or performing tasks requiring alertness until the patient knows how PEARINDA PLUS 8 affects them.

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.

The most commonly reported adverse reactions with perindopril and indapamide given separately are decreased appetite, dizziness, headaches, paraesthesia, vertigo, dysgeusia, visual impairment, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, epigastric pain, diarrhoea, dyspepsia, nausea, vomiting, dry mouth, pruritus, rash, maculopapular rash, muscle cramps and asthenia.

Tabulated list of adverse effects

Side effects for PEARINDA PLUS 8:

PROFESSIONAL INFORMATION (APPROVED)

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Rhinitis
Blood and lymphatic system disorders	Less frequent	Leukopenia, decrease in haemoglobin and haematocrit, bone marrow depression, neutropenia, anaemia, aplastic anaemia, thrombocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity/angioedema reactions, anaphylaxis 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

PROFESSIONAL INFORMATION (APPROVED)

Metabolism and nutrition disorders	Frequent Less frequent	Hypokalaemia, decreased appetite Hyperkalaemia, hyponatraemia, hypovolaemia, dehydration, increases in blood urea and blood glucose, increases in serum creatinine, raised plasma calcium levels, hypochloraemic alkalosis, indapamide may precipitate secondary gout, hypercalcaemia, hypoglycaemia
Psychiatric disorders	Less frequent	Mood alterations, sleep disturbances, mental confusion
Nervous system disorders	Frequent Less frequent Frequency unknown	Headache, dizziness, paraesthesia, vertigo Asthenia Syncope, somnolence
Eye disorders	Frequent Frequency unknown	Vision disturbance, visual impairment Myopia, blurred vision
Ear and labyrinth disorders	Frequent	Tinnitus

PROFESSIONAL INFORMATION (APPROVED)

Cardiac disorders	Less frequent Frequency unknown	Myocardial infarction and cerebrovascular accident (stroke), possibly secondary to excessive hypotension in high-risk patients, palpitations, dysrhythmia including bradycardia, ventricular tachycardia, atrial fibrillation, angina pectoris *Torsades de pointes* (potentially fatal)
Vascular disorders	Frequent	Orthostatic effects, including hypotension
Respiratory, thoracic, and mediastinal disorders	Frequent Less frequent	Dry cough, dyspnoea Bronchospasm, sinusitis, eosinophilic pneumonia, pneumonitis, acute pulmonary oedema
Gastrointestinal disorders	Frequent Less frequent	Diarrhoea, nausea, abdominal pain, indigestion, vomiting, taste disturbances, dry mouth, constipation, epigastric pain, anorexia Pancreatitis
Hepatobiliary disorders	Less frequent Frequency unknown	Jaundice, increases in liver enzymes, increases in serum bilirubin, hepatitis (hepatocellular or cholestatic) Hepatic encephalopathy

PROFESSIONAL INFORMATION (APPROVED)

Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Pruritus, maculopapular eruptions, skin rash Urticaria, diaphoresis, alopecia, psoriasis, severe skin disorders including pemphigus, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, photosensitivity or other dermatological manifestations, purpura, possible aggravation of pre-existing acute disseminated lupus erythematosus, vasculitis, pseudoporphyria, hyperhidrosis Pemphigoid
Musculoskeletal, connective tissue and bone disorders	Frequent	Muscle cramps
Renal and urinary disorders	Less frequent	Uraemia, oliguria, anuria, renal dysfunction, renal insufficiency, proteinuria, acute renal failure
Reproductive system and breast disorders	Less frequent	Impotence, erectile dysfunction
General disorders and administrative site conditions	Less frequent	Sweating, chest pain, malaise, peripheral oedema, pyrexia, fatigue
Investigations	Frequency unknown	Electrocardiogram QT prolonged, increased blood uric acid, fall, increased blood bilirubin

PROFESSIONAL INFORMATION (APPROVED)

Side effects for Perindopril:

System Organ Class	Frequency	Side effects
Infections and Infestations	Less frequent	Rhinitis
Blood and lymphatic system disorders	Less frequent	Eosinophilia, agranulocytosis, pancytopenia, leukopenia, neutropenia (see section 4.4), haemolytic anaemia, thrombocytopenia (see section 4.4)
Endocrine disorders	Frequency unknown	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Less frequent	Hyperkalaemia, reversible on discontinuation (see section 4.4), hyponatraemia (see section 4.4), hypoglycaemia
Psychiatric disorders	Less frequent	Mood altered, sleep disorder, confusion, depression
Nervous system disorders	Frequent Less frequent Frequency unknown	Dizziness, headache, paraesthesia, dysgeusia Somnolence, syncope, stroke possibly secondary to excessive hypotension in high risk patients (see section 4.4)
Eye disorders	Frequent	Visual impairment
Ear and labyrinth disorders	Frequent	Vertigo, tinnitus

PROFESSIONAL INFORMATION (APPROVED)

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)
Vascular disorders	Frequent Less frequent	Hypotension (and effects related to hypotension) (see section 4.4) Vasculitis, Raynaud's phenomenon, flushing
Respiratory, thoracic, and mediastinal disorders	Frequent Less frequent	Cough (see section 4.4), dyspnoea Bronchospasm, eosinophilic pneumonia
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting Dry mouth, pancreatitis
Hepatobiliary disorders	Less frequent	Hepatitis (see section 4.4)
Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus, rash Urticaria, angioedema (see section 4.4), hyperhidrosis, photosensitivity reaction, pemphigoid, psoriasis aggravation, erythema multiforme

PROFESSIONAL INFORMATION (APPROVED)

Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Muscle cramps Arthralgia, myalgia
Renal and urinary disorders	Less frequent	Renal insufficiency, acute renal failure, anuria/oliguria
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 decreased, haematocrit decreased (see section 4.4)
Injury and poisoning	Less frequent	Fall

Side effects for Indapamide:

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Agranulocytosis (see section 4.4), aplastic anaemia, leukopenia, haemolytic anaemia, thrombocytopenia (see section 4.4)

PROFESSIONAL INFORMATION (APPROVED)

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	Hypercalcaemia, hypochloraemia, Hypomagnesaemia, hyponatraemia, potassium depletion with hypokalaemia (particularly serious in certain high risk populations) (see section 4.4)
Nervous system disorders	Less frequent Frequency unknown	Headache, paraesthesia Syncope, Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4)
Eye disorders	Frequency unknown	Visual impairment, myopia (see section 4.4), vision blurred, acute angle-closure glaucoma, choroidal effusion
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) (see section 4.4 and 4.5)
Vascular disorders	Less frequent	Hypotension (and effects related to hypotension) (see section 4.4)
Gastrointestinal disorders	Less frequent	Constipation, nausea, vomiting, dry mouth, pancreatitis

PROFESSIONAL INFORMATION (APPROVED)

Hepatobiliary disorders	Less frequent Frequency unknown	Hepatic function abnormal Hepatitis (see section 4.4)
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Rash maculo-papular Urticaria, angioedema (see section 4.4), purpura, toxic epidermal necrolysis, Stevens Johnson syndrome Photosensitivity
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Possible worsening of pre existing acute disseminated lupus erythematosus, muscle spasms, muscular weakness, myalgia, rhabdomyolysis
Renal and urinary disorders	Less frequent	Acute renal failure
Reproductive system and breast disorders	Less frequent	Erectile dysfunction
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 (see sections 4.4 and 4.5)

Reporting of suspected adverse reactions

PROFESSIONAL INFORMATION (APPROVED)

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 following the links: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ or https://www.sahpra.org.za/Publications/Index/8. 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:

The most likely adverse reaction in cases of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria which may progress to anuria (due to hypovolaemia). Other symptoms associated with overdosage of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Salt and water disturbances (low sodium levels, low potassium levels) may occur.

Management of overdose:

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 supine position with the head lowered. If necessary, an intravenous infusion may be used.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

ATC code: C09BA04 perindopril and diuretics

Pharmacological classification: A 7.1.3 Other hypotensives.

Mechanism of action

PEARINDA PLUS 8 is a combination of perindopril tert-butylamine, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic.

The 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 components when combined.

Perindopril:

Perindopril inhibits angiotensin I-converting enzyme (ACE) activity through its active metabolite, perindoprilat. The other metabolites are inactive. 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 by the adrenal cortex. Decreased angiotensin II levels results in a decrease in vasopressor activity, increased plasma renin activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium.

Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). A reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours.

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

Indapamide:

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides.

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

5.2 Pharmacokinetic properties

Perindopril

Absorption:

Perindopril is well absorbed after oral doses with a bioavailability of about 65 to 75 % and reaching peak plasma concentration within 1 hour. Perindopril is a pro-drug and 30 to 50 % of systemically available perindopril is transformed to the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields inactive metabolites (glucuronides of perindopril and perindoprilat, dehydrated perindopril, and diastereomers of dehydrated perindoprilat). Peak plasma

concentrations of perindoprilat are achieved within 3 to 4 hours of an oral dose of perindopril and peak pharmacological activity is obtained within 4 to 6 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 (see section 4.2).

Distribution:

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

Biotransformation:

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

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.

Elimination of perindoprilat is slower in the elderly, as well as in patients with heart failure. In such patients, dosage adjustment should be made in relation to the degree of reduction in creatinine clearance. Dialysis clearance of perindoprilat is equal to 70 mL/min.

Perindoprilat excretion is decreased in renal impairment. Both perindopril and perindoprilat are removed by dialysis.

PROFESSIONAL INFORMATION (APPROVED)

Dosage adjustment in renal insufficiency patients is desirable depending on the degree of impairment (creatinine clearance) (see section 4.2). Perindopril kinetics is 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.

Linearity/non-linearity:

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

Pharmacokinetics in special patient groups:

Elderly

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

Patients with renal impairment

As plasma exposure to perindoprilat (AUC) is significantly increased in patients with moderate 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.

In patients with 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.

Paediatric population

PROFESSIONAL INFORMATION (APPROVED)

The safety and efficacy of perindopril (as contained in PEARINDA PLUS 8) in children, alone or in combination have not been established (see section 4.4).

Indapamide

Absorption:

Indapamide is well absorbed from the digestive tract. The peak plasma level is reached in humans approximately one hour after oral administration of the product.

Distribution:

Indapamide is strongly bound to plasma proteins. Plasma protein binding is 79 %.

Biotransformation and elimination:

Indapamide is extensively metabolised in the liver.

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.

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.

Pharmacokinetics in special patient groups:

Patients with renal impairment

The pharmacokinetics are unchanged in patients with renal insufficiency.

5.3 Preclinical safety data

Not applicable.

PROFESSIONAL INFORMATION (APPROVED)

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

36 months

6.4 Special precautions for storage

Store at or below 30˚C in a dry place.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

The tablets are packed in silver polyamide, aluminium, and PVC blisters. The tablets are packed as 30 tablets into a cardboard box.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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PROFESSIONAL INFORMATION (APPROVED)