

PEARINDA PLUS 4

SCHEDULING STATUS [S]

1. NAME OF THE MEDICINE PEARINDA PLUS 4 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PEARINDA PLUS 4: Each tablet contains 4 mg perindopril terbutylamine 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 tablets.

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 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/min. No dosage adjustment is necessary in patients with a creatinine clearance greater than 60 mL/min.

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.

Mixed dose

Doctors should advise patients who forgot 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 low-molecular 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
- acute 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).

Caution 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 receptor blockers or aliskiren may increase the risk of hypotension and hyperkalaemia and decrease 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 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 inhibitor 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/or other complicating factors, neutropenia rarely occurs. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant treatment, treatment with alcohol or procainamide, or a combination of these complicating factors, especially if there is pre-existing organ dysfunction. 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 sections 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 potential for 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 local or externally swelling or difficulty in swallowing or breathing, require immediate medical attention, because of the risk of angioedema with PEARINDA PLUS 4 should be discontinued.

Patients with a previous history of angioedema, which was not linked to taking an ACE inhibitor, have an increased risk of angioedema with treatment 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, ultrasound and with surgery. Symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitor 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 oropharynx 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 sections 4.3 and 4.5). Concomitant use of other neutral endopeptidase (NEP) inhibitors (e.g. ramaprilactam) 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. ramaprilactam) in patients on perindopril.

Fluoroquinolones and ACE inhibitor/renin ARBs:

Concomitant use of fluoroquinolones and ACE inhibitors/ARBs, such as PEARINDA PLUS 4, may precipitate acute kidney injury in patients at risk for possible renal impairment. PEARINDA PLUS 4 and ACE inhibitors (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 desensitisation protocols involving penicillin for penicillin allergy. PEARINDA PLUS 4 should be used with caution in allergic patients treated with desensitisation and avoided in those undergoing penicillin 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 with PEARINDA PLUS 4 for at least 24 hours before treatment in 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. AN696) 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 case 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 impairment.

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, PEARINDA 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 patients with 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:

In acute hypotension associated with electrolyte depletion in 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 in patients with hypotension or dehydration. If necessary, the patient should be placed in the supine position and if necessary receive an intravenous infusion of 0.9 % saline.

Tolerating 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.

Plasma levels:

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

Cardiovascular disease or ischaemic heart disease:

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

Blood area and serum creatinine:

Increases in blood area and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially in those with ischaemic heart disease or with treatment 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. 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 allergic aetiology should be considered in the event of this symptom. If an ACE inhibitor is the preferred therapy, continuation of treatment may be considered if necessary.

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, diazotic, diarrhoea or vomiting) – although it may occur in normo-volume 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 with low blood pressure and/or renal insufficiency. In these patients, PEARINDA PLUS 4 should be avoided. 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 not 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, systemic heart diseases or prior 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 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 these blockers should not be initiated in hypertensive patients with coronary insufficiency. The ACE inhibitor should be added to the beta blocker.

Patients with diabetes:

Increased risk of hypokalaemia, as well as hyperglycaemia 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 African origin 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 renal 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.

Hyperbolic 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 has not yet been established. Patients receiving PEARINDA PLUS 4 who develop jaundice or marked elevations of liver 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 with uncontrolled diabetes mellitus, renal insufficiency, malnutrition, coronary problems or heart failure, chronic patients with oedema or ascites, the elderly (> 70 years), those with life-threatening, life-threatening, 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 NSAIDs, 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), the risk of the effect is slight.

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 chronic patients (see sections 4.8 and 4.9).

Hypernatraemia with hypokalaemia 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 the 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, chronic 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 torsade 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 but sustained 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 hyperuricemic 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 below approximately 25 mL/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 Cockcroft-Gault formula. Creatinine clearance (mL/min) = $\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{plasma creatinine (mg/dL)}}$

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0.85.

Hypokalaemia, 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 area 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:

Subconjunctival or subconjunctival derivate medicines can cause an idiosyncratic reaction resulting in transient myopia and acute angle-closure glaucoma. Unfiltered 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 subconjunctival or perilymphatic use.

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:

Backlofer:

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

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

Concomitant administration of ACE inhibitors with nonsteroidal anti-inflammatory drugs (e.g. 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 patients with renal impairment (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:

Hypotensive agents, neurileptics:

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. Concomitant 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. polycarbonate 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 renin 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).

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS [53]

PEARARINDA PLUS 4 tablets

Perindopril *tert*-butylamine salt and indapamide
PEARARINDA PLUS 4: Contains sugar (lactose monohydrate 61,53 mg per tablet).

Read all of this leaflet carefully before you start taking PEARARINDA PLUS 4

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- PEARARINDA PLUS 4 has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

- What PEARARINDA PLUS 4 is and what it is used for
- What you need to know before you take PEARARINDA PLUS 4
- How to take PEARARINDA PLUS 4
- Possible side effects
- How to store PEARARINDA PLUS 4
- Contents of the pack and other information

1. What PEARARINDA PLUS 4 is and what it is used for
PEARARINDA PLUS 4 is a combination of two active ingredients, i.e. perindopril and indapamide. Perindopril belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Indapamide is a diuretic (sometimes called a water tablet). Diuretics increase the amount of urine produced by the kidneys. However, indapamide is different from other diuretics, as it only causes a slight increase in the amount of urine produced.

PEARARINDA PLUS 4 is used to treat high blood pressure (hypertension).

2. What you need to know before you take PEARARINDA PLUS 4:

Do not take PEARARINDA PLUS 4:

- if you are hypersensitive (allergic) to perindopril or any other ACE inhibitor, or to indapamide or any other sulphonamides, or to any of the ingredients of PEARARINDA PLUS 4 (see section 6)
- if you have ever had an allergic reaction such as swelling of the face, tongue or throat, wheezing, skin rashes, intense itching, dizziness or fainting with previous ACE inhibitor and/or angiotensin receptor blockers (ARBs) treatment or have had these symptoms in any other circumstances (this is a condition called angioedema); these patients should never again be given these medicines
- if you have hereditary or idiopathic angioedema
- if you have narrowing of the main blood vessel leading from the heart or heart muscle disease or narrowing of the artery supplying the kidney with blood
- if you are treated with ACE inhibitors/ARBs together with a fluorquinolone antibiotic such as ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin and norfloxacin, contact your doctor to re-evaluate your treatment
- if you have any other heart, liver or kidney problems
- if you take potassium supplements, potassium-containing salt substitutes and potassium sparing diuretics such as spironolactone, triamterene, amiloride
- if you have porphyria
- if you suffer from Addison's disease
- if you have low blood potassium levels
- if you take lithium products
- if you are preg, nursing or breastfeeding
- if you have severe liver disease or suffer from a condition called hepatic encephalopathy (degenerative disease of the brain)
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren
- if you are being treated with sacubitril/valsartan, a medicine for heart failure
- if you are receiving dialysis, or any other type of blood filtration. Depending on the machine that is used, PEARARINDA PLUS 4 may not be suitable for you.

Warnings and precautions

Take special care with PEARARINDA PLUS

PEARARINDA PLUS 4 tablets should not be given to children.

The presence of other medical problems may affect the use of PEARARINDA PLUS 4.

Tell your doctor, pharmacist or healthcare provider:

- if you take lithium for treatment of mood disorders (see Do not take PEARARINDA PLUS 4)
- if you are treated with ACE inhibitors/ARBs together with a fluorquinolone antibiotic such as ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin and norfloxacin as he/she will need to re-evaluate your treatment, or if you are elderly
- if you have high or low blood potassium, low blood sodium, or are on a sodium-restricted diet or use salt substitutes which contain potassium
- if you suffer from a collagen disease such as systemic lupus erythematosus or scleroderma, or your immune system is suppressed
- if you have problems with your kidneys or if you are receiving dialysis with high-flux membranes
- if you have a severe allergic reaction with swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema). This may occur at any time during treatment. If you develop such symptoms, you should stop taking PEARIND PLUS 4 and see a doctor immediately
- if you are taking sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTOR inhibitors (used to avoid rejection of transplanted organs)
- if you are taking sacubitril (available as fixed-dose combination with valsartan), used to treat long-term heart failure (see Do not take PEARINDA PLUS 4)
- if you are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings

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PASİENTİNİLGİTİNGİSLAD

SKEDULERİNGİSTATUS [53]

PEARARINDA PLUS 4 tablette

Perindopril *tert*-butilelamiensout en indapamid
PEARARINDA PLUS 4: Bevat suiker (laktosemonohidraat 61,53 mg per tablet).

Lees hierdie hele inligtingsblad deeglik deur, voordat u begin om PEARARINDA PLUS 4 te neem.
Om hierdie inligtingsblad. Dit mag nodig wees vir u om dit weer te lees.

- Indien u verdere vrae het, vra asseblief u dokter, apteker, verpleegkundige of ander gesondheidsorgverskaffer.
- PEARARINDA PLUS 4 is vir u persoonlik voorgeskryf en u moet nie u medisyne met ander mense deel nie. Dit mag skadelik wees vir hulle, selfs al is hulle sinne dieselfde as u eie.

Inhoud van hierdie inligtingsblad

- Wat PEARARINDA PLUS 4 is en waarvoor dit gebruik word
- Wat u nodig het om te weet, voordat u PEARARINDA PLUS 4 neem
- Hoe om PEARARINDA PLUS 4 te neem
- Moontlike newe-effekte
- Hoe om PEARARINDA PLUS 4 te bewaar
- Verpakkingsinhoud en ander inligting

1. Wat PEARARINDA PLUS 4 is en waarvoor dit gebruik word

PEARARINDA PLUS 4 is 'n kombinasie van twee aktiewe bestanddele, d.i. perindopril en indapamid. Perindopril behoort aan 'n klas medisyne wat AOE-remmers genoem word. Dit werk deur bloedvate te verwyd en u hart se vermoë om bloed daardeur te pomp, te verminder.

Indapamid is 'n diuretikum (somsyds "n wateratletiek geneem). Diuretika verhoog die volume urine wat deur die niere vervaardig word. Dit verskaf spesiale effekter van ander diuretika, aangesien dit slegs 'n effense verhoging in urineproduksie veroorsaak.

PEARARINDA PLUS 4 word gebruik om hoë bloeddruk (hipertensie) te behandel.

2. Wat u nodig het om te weet, voordat u PEARARINDA PLUS 4 neem

Moet nie PEARARINDA PLUS 4 neem:

- indien u hipersensitief (allergies) is vir perindopril, of enige ander AOE-remmer, of vir indapamid, of vir enige ander sulfoonamide, of vir enige ander bestanddele van PEARARINDA PLUS 4 nie (sien afdeling 6)
- indien u ooit simptome soos swelling van die gesig, tong of keel, huijslag, intensie geies, duiiseligheid of floute, met vorige AOE-remmers, en/ of angiotensienreseptorblokkers (ARBs) en/or ander nie, of herties simptome gehad het en/or ander ander omstandighede nie (hierdie is "n toestand wat angioedeem genoem word). Hierdie pasiënte moet nooit weer hierdie medisyne gebruik nie
- indien u aan oorertlike, of idiopatiese angio-eedem ly nie
- indien u 'n vermying van die hoofaar wat die hart, of hartspiesiekte, of 'n vermying van die arterie wat bloed na die niere voorsien, het nie
- kontak u dokter om u behandeling te herewealer, indien u ook met AOE-remmers/ARBs, saam met 'n fluoorkinoloon antibiotikum, soos siprofloksasien, gemfloksiasien, levofloksiasien, moksifloksiasien en norfloksiasien, behandel word
- indien u 'n erge alergie hart-, lever-, of nierprobleme ly nie
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- indien u porfirie het nie
- indien u aan Addison se siekte ly nie
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- indien u litiumprodukte neem nie
- indien u swanger is of borsvoed nie
- indien u 'n erge lewersiekte het, of aan toestand wat hepatiese encefalopatie genoem word, ly nie (degeneratiewe breinsiekte)
- indien u diabetes, of belemmerde nierfunksie het en u met bloeddruk-verlagende medisyne wat aliskiren bevat, behandel word nie
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- indien u aan Addison se siekte ly nie
- indien u lae kaliumvlakke het nie
- indien u litiumprodukte neem nie
- indien u swanger is of borsvoed nie
- indien u 'n erge lewersiekte het, of aan toestand wat hepatiese encefalopatie genoem word, ly nie (degeneratiewe breinsiekte)
- indien u diabetes, of belemmerde nierfunksie het en u met bloeddruk-verlagende medisyne wat aliskiren bevat, behandel word nie
- indien u met sakubitril/valsartan behandel word nie ("n medisyne vir hartversaking)
- indien u 'n vermying van die hoofaar wat die hart, of hartspiesiekte, of 'n vermying van die arterie wat bloed na die niere voorsien, het nie
- kontak u dokter om u behandeling te herewealer, indien u ook met AOE-remmers/ARBs, saam met 'n fluoorkinoloon antibiotikum, soos siprofloksasien, gemfloksiasien, levofloksiasien, moksifloksiasien en norfloksiasien, behandel word
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