

PEARINDA 4

PEARINDA 8

SCHEDULING STATUS S3

PROPRIETY NAME AND DOSAGE FORM

PEARINDA 4 Tablet

PEARINDA 8 Tablet

COMPOSITION

Each **PEARINDA 4** tablet contains 4 mg perindopril *tert*-butylamine salt.

Each **PEARINDA 8** tablet contains 8 mg perindopril *tert*-butylamine salt.

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION

Perindopril inhibits angiotensin converting enzyme (ACE) activity through its active metabolite, perindoprilat. It is a specific non-sulphydryl competitive ACE inhibitor. It inhibits the conversion of the relatively inactive angiotensin I to angiotensin II.

Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels results in a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium.

It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

Pharmacokinetics

Absorption

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

Distribution

Perindopril and perindoprilat have a low volume of distribution. The plasma protein binding of perindoprilat is weak (about 10 to 20%).

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

INDICATIONS

PEARINDA is indicated for:

- Mild to moderate hypertension.
- Congestive heart failure not adequately controlled by conventional therapy with digitalis and diuretics, and in whom vasodilatation is indicated.

CONTRA-INDICATIONS

- Sensitivity to any of the components of **PEARINDA**.
- Patients with a history of angioedema related to previous ACE-inhibitor therapy or angiotensin receptor blocker (ARB): These patients should never again be given this medication.
- Hereditary or idiopathic angioedema.
- Aortic stenosis.
- Hypertrophic obstructive cardiomyopathy.
- Severe renal function impairment (creatinine clearance below 30 ml/min).
- Bilateral renal stenosis or renal artery stenosis in patients with a single kidney.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.
- Thiazide diuretics, such as **PEARINDA**, should not be given to patients with Addison's disease. They are also contra-indicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.
- Lithium: Concomitant administration with **PEARINDA** may lead to a toxic blood concentration of lithium.

- Pregnancy and lactation (see “**PREGNANCY AND LACTATION**”).

WARNINGS

Should a woman become pregnant while receiving **PEARINDA**, the treatment must be stopped promptly and changed to a different medicine (see “**PREGNANCY AND LACTATION**”).

If a woman is contemplating pregnancy, a different class of medicine should be used (see “**PREGNANCY AND LACTATION**”).

PEARINDA should be used with caution in the following conditions:

- Cerebrovascular disease or ischaemic heart disease - reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular accidents.
- Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting) – although it may occur in normo-volaemic 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** induced renal failure, especially in those with congestive heart failure.
- Patients at a high risk of symptomatic hypotension e.g. patients with salt or volume depletion with or without hyponatraemia should have these conditions corrected before therapy with **PEARINDA**. Monitoring is required after initiating therapy.
- Autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma, increase the risk for development of neutropenia or agranulocytosis.
- In acute myocardial infarction, treatment with **PEARINDA** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 mmol/L or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 mmol/L or doubling of the pre-treatment value) then **PEARINDA** may need to be withdrawn (also see “**CONTRA-INDICATIONS**”).
- In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.
- Hypotension in acute myocardial infarction - treatment with **PEARINDA** must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 100 mmHg 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 for more than 1 hour) then **PEARINDA** should be withdrawn.

- Bone marrow depression – increased risk of agranulocytosis and neutropaenia.
- Diabetes mellitus - increased risk of hyperkalaemia, as well as hypoglycaemia may occur.
- Hyperkalaemia - **PEARINDA** may cause an increase in serum potassium levels. The following patients are at risk for the development of hyperkalaemia: those with uncontrolled diabetes mellitus, renal insufficiency, those using concomitant potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes; or those patients on other medication associated with increases of serum potassium (e.g. heparin). Regular monitoring of serum potassium is recommended, if concomitant use of the abovementioned agents is deemed appropriate. Also see “**INTERACTIONS**”.
- Renovascular disease - **PEARINDA** should not be used in patients with renovascular disease or suspected renovascular disease but it may be used cautiously in severe resistant hypertension in such patients. In this instance **PEARINDA** should only be used under specialist supervision. The elderly and patients with peripheral vascular diseases or generalised atherosclerosis may have asymptomatic renovascular disease (see “**DOSAGE AND DIRECTIONS FOR USE**”).
- Renal artery stenosis, bilateral or in one kidney or renal transplant - increased risk of renal function impairment may cause increases in blood urea and serum creatinine concentrations, which may be reversible upon discontinuation of therapy. There is also an increased risk of agranulocytosis and neutropenia when immunosuppressants are concurrently administered (see “**CONTRA-INDICATIONS**”).
- Renal function impairment – decreased elimination of **PEARINDA** resulting in an increased risk of hyperkalaemia. These patients may require lower doses.
- Anaphylactoid reaction have occurred in patients using ACE inhibitors, including **PEARINDA**, during desensitising protocols involving, for example, hymenoptera venom.
- Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulphate absorption.

- Hypersensitivity/Angioedema - if angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients treated with **PEARINDA**, **PEARINDA** should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms (see “**CONTRA-INDICATIONS**”).
- 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, ACE-Inhibitors or angiotensin-receptor blockers again** (see “**CONTRA-INDICATIONS**”).
- **PEARINDA** causes a higher rate of angioedema in black patients than in non-black patients.
- Safety and efficacy in children has not been established.
- Concomitant therapy with 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.
- ACE-inhibitors pass through the placenta and can be presumed to cause disturbances in foetal blood pressure regulatory mechanisms. Oligohydromnios, as well as hypotension, oligouria and anuria in newborns have been reported after administration of ACE-inhibitors such as **PEARINDA** in the second and third trimesters. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.

INTERACTIONS

Concomitant use of **PEARINDA** with: -

- Diuretics, alcohol, anti-hypertensive and other hypotension-producing medications – the antihypertensive effect is additive. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.
- Loop, thiazide or related diuretics – “first dose hypotension” may occur (see “**DOSAGE AND DIRECTIONS FOR USE**”).
- Indomethacin and nonsteroidal anti-inflammatory medicines (NSAID’s) – reduce the antihypertensive effects of **PEARINDA**. Blood pressure

monitoring should be increased when any NSAID is added or discontinued in a patient treated with **PEARINDA**.

- Potassium supplements or potassium sparing diuretics such as spironolactone, triamterene or amiloride – concurrent administration may result in hyperkalaemia.
- Lithium (see “**CONTRA-INDICATIONS**”).

PREGNANCY AND LACTATION

PEARINDA is contra-indicated during pregnancy. ACE-inhibitors can cause foetal morbidity and death.

Safety in lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

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

Mild to moderate hypertension

The recommended starting dosage is 4 mg once daily. This can be increased to 8 mg once daily after one month of treatment, if necessary.

Patients with renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension may experience an excessive drop in blood pressure following the initial dose. It is recommended that initiation of treatment should take place under medical supervision, using a starting dose of 2 mg in such patients.

In elderly patients treatment should be initiated at a dose of 2 mg which may be increased according to response to a maximum of 8 mg daily.

Patients with type I and type II diabetes mellitus may be treated with the usual doses.

Concomitant use of diuretics in hypertension

Caution is advised in patients on current diuretic treatment. The effects of **PEARINDA** may be potentiated in a situation where hypovolaemia may occur.

Patients taking diuretics should therefore have the diuretic withdrawn 2 to 3 days before beginning therapy with **PEARINDA**, and resumed later if required. If this is not possible, an initial dose of 2 mg may be given.

When concomitant use of diuretics is indicated, it is recommended that the serum potassium should be monitored before prescribing a potassium salt or a potassium sparing diuretic.

Congestive heart failure

Treatment should be initiated at a low dose under close medical supervision. The initial dose is 2 mg as a single dose in the morning. This may be increased to 4 mg once daily as a maintenance dose.

Renal insufficiency

The dosage of **PEARINDA** should be adjusted in relation to the severity of renal insufficiency. The dosage recommendations are:

<i>Creatinine clearance</i>	<i>Recommended dosage</i>
Between 30 and 60 ml/min	2 mg per day
Between 15 and 30 ml/min	2 mg on alternate days
Less than 15 ml/min	2 mg on the day of dialysis*

* The mean dialysis clearance of perindopril is 52 ml/minute and that of perindoprilat 67,2 ml/minute.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side Effects

The following undesirable effects have been observed during treatment with **PEARINDA** and ranked under the following frequency:

Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10000$, $< 1/1000$); very rare ($< 1/10000$), including isolated reports.

Haematological disorders

Very rare: Decreases in white blood cell count, haemoglobin and haematocrit, bone marrow depression, anaemia, thrombocytopaenia, agranulocytosis, haemolytic anaemia.

Cardiovascular disorders

Common: Orthostatic effects, including hypotension.

Very rare: Myocardial infarction, cerebrovascular accident, palpitations, tachycardia, chest pain.

Neurological disorders

Common: Dizziness, headache, paraesthesia, vertigo, fatigue.

Uncommon: Mood alterations, sleep disturbances.

Very rare: Mental confusion.

Endocrine/Metabolic disorders

Very rare: Hyperkalaemia, hyponatraemia, increases in blood urea, increases in serum creatinine.

Gastrointestinal disorders

Common: Diarrhoea, nausea, abdominal pain, indigestion, vomiting, taste disturbances, constipation.

Uncommon: Dry mouth.

Very rare: Pancreatitis.

Kidney/Genitourinary disorders

Uncommon: Impotence.

Very rare: Uraemia, oligouria, anuria, renal dysfunction, acute renal failure.

Liver/hepatic disorders

Rare: Jaundice, increases in liver enzymes, increases in serum bilirubin.

Very rare: Hepatitis (hepatocellular or cholestatic).

Musculoskeletal disorders

Common: Asthenia, muscle cramps.

Respiratory disorders

Common: Cough, dyspnoea.

Uncommon: Bronchospasm.

Very rare: Rhinitis, sinusitis, eosinophilic pneumonia.

Skin disorders

Common: Rash, pruritus.

Uncommon: Urticaria, sweating.

Very rare: Diaphoresis, alopecia, psoriasis, severe skin disorders including pemphigus, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. Rash, photosensitivity or other dermatological manifestations may occur.

Other

Common: Vision disturbance, tinnitus.

Uncommon: Hypersensitivity/angioedema reactions: angioedema of the face, extremities, lips, tongue, glottis and/or larynx, which may be fatal.

Rare: Intestinal angioedema.

Very rare: A symptom complex has been reported which may include: fever, vasculitis, myalgia, arthritis/arthritis, a positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis.

Special Precautions:

- Myocardial infarction and cerebrovascular accidents may be due to severe falls in blood pressure in high-risk patients e.g. those with ischaemic heart disease or cerebrovascular disease.

- In volume depleted patients or patients with ischaemic heart disease or cerebrovascular disease, therapy should be monitored especially when the dose of **PEARINDA** or diuretic is adjusted.
- If hypotension occurs, the patient should be placed in the supine position and if necessary receive an intravenous infusion of 0,9% saline.
- Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when **PEARINDA** has been given concomitantly with a diuretic. Dosage reduction or discontinuation of **PEARINDA** or the diuretic may be required.
- Signs of facial or extremity swelling or difficulty in swallowing or breathing, require immediate medical attention, because of the risk of angioedema. **PEARINDA** should be discontinued. Such a patient should never receive any **PEARINDA**, ACE-Inhibitors or angiotensin-receptor blockers again.
- Caution is advised when driving or performing tasks requiring alertness because of possible dizziness.
- In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, **PEARINDA** may block angiotensin II formation secondary to complementary renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.
- Renal function impairment - decreased elimination of **PEARINDA** resulting in an increased risk of hyperkalaemia. These patients may require lower doses.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See "**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**")

Symptoms of overdose

Severe hypotension, electrolyte disturbances and renal failure.

Treatment of overdose

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

IDENTIFICATION

PEARINDA 4: A white capsule shaped tablet, with dimensions of 8 x 4 mm approx., bearing a breakline on both sides.

PEARINDA 8: A white round convex tablet, with a diameter of 8 mm approx., bearing a breakline on one side.

PRESENTATION

PEARINDA 4: The tablets are available in PA-Alu-PVC/Alu foil blister packs of 30's.

PEARINDA 8: The tablets are available in PA-Alu-PVC/Alu foil blister packs of 30's.

STORAGE INSTRUCTIONS

Store below 25°C.

Keep the blisters in the carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS

PEARINDA 4: 41/7.1.3/0649

PEARINDA 8: 41/7.1.3/0650

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Marketed by **PHARMA DYNAMICS (PTY) LTD** for:

Specpharm (Pty) Ltd

Cnr 15th & Pharmaceutical Road

Halfway House

Midrand

DATE OF PUBLICATION OF PACKAGE INSERT

April 2009

PEARINDA 4

PEARINDA 8

SKEDULERINGSSTATUS S3

EIENDOMSNAAM EN DOSEERVORM

PEARINDA 4 Tablet

PEARINDA 8 Tablet

SAMESTELLING

Elke PEARINDA 4 tablet bevat 4 mg perindopriël *tert*-butielamiensout .

Elke PEARINDA 8 tablet bevat 8 mg perindopriël *tert*-butielamiensout .

FARMAKOLOGIESE KLASSIFIKASIE

A 7.1.3 Ander hipotensiewe middels.

FARMAKOLOGIESE WERKING

Perindopriël inhibeer angiotensien omsettingsensiem (AOE)-aktiwiteit deur die aktiewe metaboliet, perindopriëlaat. Dit is 'n spesifieke nie-sulfhidriël mededingende AOE-inhibeerder. Dit inhibeer die omsetting van die relatief onaktiewe angiotensien I na angiotensien II. Angiotensien II is 'n kragtige vasokonstriktor en stimuleer die vrystelling van aldosteroon. Laer angiotensien II-vlakke lei tot 'n afname in vasopressoraktiwiteit en 'n afname in aldosteroonsekresie, wat kan lei tot klein toenames in serumkalium.

Daar word ook gemeen dat AOE-inhibering moontlik degradering van bradikiniën kan inhibeer, wat aanleiding kan gee tot verhoogde bradikiniënvlakke.

Farmakokinetika

Absorpsie

Perindopriël word vinnig geabsorbeer ná orale dosisse met 'n biobeskikbaarheid van nagenoeg 65 tot 75%, en bereik piekplasmakonsentrasie binne 1 uur. Piekplasmakonsentrasies van perindopriëlaat word binne 3 tot 4 uur ná 'n orale dosis perindopriël bereik. Die tyd tot piekeffek is 3 tot 7 uur. Die aanwesigheid van voedsel beïnvloed nie die tempo of omvang van absorpsie van perindopriël nie, maar daar word gemeld dat dit die omsetting van perindopriël na perindopriëlaat verlaag.

Verspreiding

Perindopriël en perindopriëlaat het 'n lae volume van distribusie. Die plasma-proteïenbinding van perindopriëlaat is swak (sowat 10 tot 20%).

Biotransformasie

Perindopriël word omvattend in die lewer gemetaboliseer na perindopriëlaat en onaktiewe metaboliete, insluitende glukuroniede.

Eliminasie

Perindopriël word hoofsaaklik in die urine uitgeskei as onveranderde perindopriël (die eliminasiehalfleeftyd is ongeveer 1 uur), as perindopriëlaat, en as ander metaboliete.

Die oorblywende gedeelte word in die feses uitgeskei. Perindopriëlaat het 'n

tweefasige eliminasië met 'n distribusiehalfleeftyd van ongeveer 5 uur en 'n

eliminasiëhalfleeftyd van 25 tot 30 uur of langer. Laasgenoemde halfleeftyd

verteenwoordig waarskynlik sterk binding aan angiotensienomsettingsensiem.

Perindopriëlaatuitskeiding is verlaag in die geval van verswakte nierfunksie. Beide perindopriël en perindopriëlaat word deur dialise verwyder.

INDIKASIES

PEARINDA word aangedui vir:

- Ligte tot matige hipertensie.
- Kongestiewe hartversaking wat nie voldoende beheer word deur konvensionele terapie met digitalis en diuretika nie, en waarby vasodilasie nodig is.

KONTRA-INDIKASIES

- Sensitiwiteit vir enige van die bestanddele van **PEARINDA**.
- Pasiënte met 'n geskiedenis van angio-edeem wat verband hou met vorige AOE-inhibeerderbehandeling of angiotensienreseptor-blokkeerders (ARB): Hierdie medisyne moet nooit weer aan hierdie pasiënte gegee word nie.
- Oorerflike of idiopatiese angio-edeem.
- Aortiese stenose.
- Hipertrofiese obstruktiwê kardiomiopatie.
- Erge ontoereikende nierfunksie (kreatinienopruiming benede 30 ml/min).
- Bilaterale renale stenose of renale arteriëstenose by pasiënte met 'n enkele nier.
- Gelyktydige behandeling met kaliumbesparendediuretika soos spironolaktoon, triamteren, amiloried.
- Porfirie.
- Tiasieddiuretika, soos **PEARINDA**, moet nie aan pasiënte met Addison se siekte gegee word nie. Dit is ook teenaangedui in pasiënte met erge verswakte nierfunksie of anurie, en by pasiënte wat hipersensitiwiteit toon teenoor ander sulfonamied-afgeleide medisyne.

- Litium: Gelyktydige toediening met **PEARINDA** kan tot 'n toksiese bloedkonsentrasie litium lei.
- Swangerskap en laktasie (sien “**SWANGERSKAP EN LAKTASIE**”).

WAARSKUWINGS

Indien 'n vrou sou swanger raak terwyl sy **PEARINDA** ontvang, moet die behandeling onmiddellik gestaak word en sy na 'n ander medisyne oorgeskakel word (sien “**SWANGERSKAP EN LAKTASIE**”).

Indien 'n vrou swangerskap beplan, moet 'n ander klas medisyne gebruik word (sien “**SWANGERSKAP EN LAKTASIE**”).

PEARINDA moet met omsigtigheid by die onderstaande toestande gebruik word:

- Serebrovaskulêre siekte of iskemiese hartsiekte – afname in bloeddruk kan hierdie toestande vererger en kan lei tot miokardiale infarksie en serebrovaskulêre episodes.
- Pasiënte met volume-uitputting (bv. tydens diuretikumbehandeling, tydens dieet met beperkte soutinname, dialise, diarree of braking) – alhoewel dit by pasiënte met normale volume kan voorkom, kom hipotensie meer gereedelik by pasiënte met uitgeputte volume voor. 'n Skielike afname in angiotensien II kan tot skielike en erge hipotensie lei. Daar is ook 'n hoër risiko van **PEARINDA**-geïnduseerde nierversaking, in die besonder by diegene met kongestiewe hartversaking.
- Pasiënte met 'n hoë risiko van simptomaties hipotensie, bv. pasiënte met sout- of volume-uitputting met of sonder hiponatremie, moet hierdie toestande laat regstel voor behandeling met **PEARINDA**. Monitering is ná aanvang van behandeling nodig.
- Auto-immuunsiekte, in die besonder sistemiese lupus eritematose, ander kollageen- vaskulêre siekte of scleroderma, verhoog die risiko vir die ontwikkeling van neutropenie of agranulose.
- Tydens akute miokardiale infarksie moet behandeling met **PEARINDA** nie begin word by pasiënte met bewyse van nierdisfunksie (serumkreatinienkonsentrasie hoër as 177 mmol/L of proteïnurie hoër as 500 mg/24 uur) nie. Indien nierdisfunksie tydens behandeling ontwikkel (serumkreatinienkonsentrasie hoër as 177 mmol/L of verdubbeling van die waarde voor die behandeling) moet **PEARINDA** waarskynlik onttrek word (sien ook “**KONTRA-INDIKASIES**”).
- By akute miokardiale infarksie kan pasiënte aanhoudende hipotensie en/of verswakte nierfunksie ontwikkel.
- Hipotensie by akute miokardiale infarksie – behandeling met **PEARINDA** moet nie begin word by pasiënte met akute miokardiale infarksie wat die gevaar loop

van verdere ernstige hemodinamiese agteruitgang ná behandeling met 'n vasodilator nie. Dit sluit in pasiënte met sistoliese bloeddruk van 100 mmHg of laer of kardiogeniese skok. Tydens die eerste 3 dae ná die infarksie moet die dosis verminder word indien die sistoliese bloeddruk 120 mmHg of laer is. Instandhoudingsdosisse moet verminder word indien sistoliese bloeddruk 100 mmHg of laer is. Indien hipotensie voortduur (sistoliese bloeddruk minder as 90 mmHg vir langer as 1 uur) moet **PEARINDA** onttrek word.

- Beenmurgonderdrukking – verhoogde risiko van agranulotose en neutropenie.
- Diabetes mellitus – verhoogde risiko van hiperkalemie, en hipoglisemie kan moontlik voorkom.
- Hiperkalemie – **PEARINDA** kan 'n verhoging in serumkaliumvlakke veroorsaak. Die volgende pasiënte kan moontlik hiperkalemie ontwikkel: diegene met onbeheerde diabetes mellitus, nierontoereikendheid, diegene wat gelyktydig kalium-aanvullings, kaliumbesparende diuretika of kaliumbevattende sout- vervangers gebruik, of daardie pasiënte op ander medikasie wat geassosieer word met toenames in serumkaliumvlakke (bv. heparien). Gereelde monitering van serumkalium word aanbeveel indien gelyktydige gebruik van die bogemelde agente as aangewese beskou word. Sien ook "**INTERAKSIES**".
- Renovaskulêre siekte – **PEARINDA** moet nie gebruik word in pasiënte met renovaskulêre siekte of vermoedelike renovaskulêre siekte nie, maar dit kan met omsigtigheid by sodanige pasiënte gebruik word tydens erge weerstandige hipertensie. In sodanige geval moet **PEARINDA** slegs gebruik word onder gespesialiseerde toesig. Bejaardes en pasiënte met perifere vasculêre siektes of algemene aterosklerose kan asimptomatiese renovaskulêre siekte hê (sien "**DOSIS EN GEBRUIKSAANWYSINGS**").
- Nieraarstenose, bilateraal of in een nier of nieroorplanting – verhoogde risiko van belemmerde nierfunksie kan toenames in bloedureum en serumkreatinienkonsentrasie veroorsaak, wat ná staking van behandeling omkeerbaar kan wees. Daar is ook 'n verhoogde risiko van agranulotose en neutropenie wanneer immuunonderdrukkers gelyktydig toegedien word. (Sien "**KONTRA-INDIKASIES**").
- Verswakte nierfunksie – verlaagde eliminasië van **PEARINDA** wat lei tot 'n verhoogde risiko van hiperkalemie. Hierdie pasiënte kan laer dosisse nodig.
- Anafilaktiese reaksies het tydens protokolle vir desensitisering met byvoorbeeld hymenoptera-gif voorgekom by pasiënte wat AOE-remmers, met inbegrip van **PEARINDA**, gebruik.

- Anafilaktiese reaksies is aangemeld by pasiënte blootgestel aan óf dialise met hoë vloedmembrane óf laedigheid lipoproteïenafereuse met dekstraansulfaat-absorpsie.
- Hipersensitiwiteit/Angio-edeem – indien angio-edeem van die gesig, ekstremitate, lippe, tong, glottis en/of larinks waargeneem word by pasiënte wat met **PEARINDA** behandel word, moet **PEARINDA** onmiddellik gestaak word. Hierdie pasiënte moet gemoniteer word om volledige opklaring van simptome te verseker.
- Angio-edeem in assosiasie met laringeale edeem kan dodelik wees. Indien die tong, glottis of larinks betrokke is kan dit moontlik lei tot lugwegobstruksie en geskikte noodbehandeling moet toegepas word. Dit kan die toediening van adrenalien en/of die ondersteuning van 'n oop lugweg insluit. Die pasiënt moet onder noukeurige mediese toesig gehou word totdat volledige en volgehoue opklaring van simptome verkry is. **Hierdie pasiënte moet nooit weer enige PEARINDA, AOE-remmers of angiotensien-reseptorblokkers ontvang nie.** (Sien “**KONTRA-INDIKASIES**”)
- **PEARINDA** veroorsaak 'n hoër voorkoms van angio-edeem in swart pasiënte as in nie-swart pasiënte.
- Veiligheid en effektiwiteit by kinders is nie vasgestel nie.
- Gelyktydige behandeling met kaliumbesparende diuretika soos spironolaktoon, triamteren en amiloried kan tot hiperkalemie lei, wat ernstig kan wees en tot abnormaliteite in geleiding van die hart, disritmieë en hartstilstand kan lei.
- AOE-remmers kruis die plasenta en daar kan aangeneem word dat dit steuringe in fetale bloeddruk-beheermeganismes veroorsaak. Oligohidromnios, asook hipotensie, oligurie en anurie by pasgeborenes is aangemeld ná toediening van AOE-remmers soos **PEARINDA** in die tweede en derde trimesters. Gevalle van defektiewe skedelossifikasie is waargeneem. Prematuriteit en lae geboortemassa kan moontlik voorkom.

INTERAKSIES

Gelyktydige gebruik van **PEARINDA** met: -

- Diuretika, alkohol, antihipertensiewe en ander hipotensie-veroorsakende medikasie – die antihipertensiewe effek is additief. Dosisaanpassings kan moontlik nodig wees tydens gelyktydige gebruik of wanneer een medisyne gestaak word.
- Lus-, tiasied- of verwante diuretika – “eerstedosishipotensie” kan moontlik voorkom (sien “**DOSIS EN GEBRUIKSAANWYSINGS**”).

- Indometasien en nie-steroïed anti-inflammatoriese middels (NSAIM's) – verminder die antihipertensiewe effekte van **PEARINDA**. Bloeddrukmonitering moet verhoog word wanneer enige NSAIM bygevoeg of gestaak word by 'n pasiënt wat met **PEARINDA** behandel word.
- Kaliumaanvullings of kaliumbesparende diuretika soos spironolaktoon, triamteren of amiloried – gelyktydige toediening kan lei tot hiperkalemie.
- Litium (sien "**KONTRA-INDIKASIES**").

SWANGERSKAP EN LAKTASIE

PEARINDA is teenaangedui tydens swangerskap. AOE-remmers kan fetale morbiditeit en dood veroorsaak.

Veiligheid tydens laktasie is nie vasgestel nie.

DOSIS EN GEBRUIKSAANWYSINGS

Daar word aanbeveel dat **PEARINDA** eenmaal daaglik in die oggend voor 'n maaltyd geneem word.

Ligte tot matige hipertensie

Die aanbevole aanvangsdosis is 4 mg eenmaal daaglik. Dit kan indien nodig verhoog word tot 8 mg eenmaal daaglik ná een maand se behandeling.

Pasiënte met renovaskulêre hipertensie, sout- en/of volume-uitputting, kardiaal dekompensasie of erge hipertensie kan moontlik ná die aanvangsdosis 'n uitermatige daling in bloeddruk ervaar. Daar word aanbeveel dat aanvang van behandeling onder mediese toesig plaasvind, met 'n aanvangsdosis van 2 mg by sodanige pasiënte.

By bejaarde pasiënte moet behandeling begin word met 'n dosis van 2 mg wat verhoog kan word volgens die reaksie tot 'n maksimum van 8 mg daaglik.

Pasiënte met tipe I en tipe 2 diabetes mellitus kan met die gewone dosisse behandel word.

Gelyktydige gebruik van diuretika in hipertensie

Omsigtigheid word aangeraai by pasiënte tans op diuretiese behandeling. Die effek van **PEARINDA** kan moontlik versterk word in hipovolemiese situasies. In pasiënte wat diuretika gebruik, moet die diuretika dus 2 tot 3 dae voor terapie met **PEARINDA** begin, onttrek word, en later hervat word indien nodig. Indien dit nie moontlik is nie, kan 'n aanvangsdosis van 2 mg gegee word.

Wanneer gelyktydige gebruik van diuretika aangedui is, word daar aanbeveel dat die serumkalium gemonitor word voor 'n kaliumsout of 'n kaliumbesparende diuretikum voorgeskryf word.

Kongestiewe hartversaking

Behandeling moet begin word teen 'n lae dosis onder noukeurige mediese toesig. Die aanvangsdosis is 2 mg as 'n enkele dosis in die oggend. Dit kan moontlik verhoog word tot 4 mg eenmaal daaglik as 'n instandhoudingsdosis.

Nierontoereikendheid

Die **PEARINDA** dosis moet aangepas word in verhouding tot die erns van die nierontoereikendheid. Die dosisaanbevelings is:

<i>Kreatinienopruiming</i>	<i>Aanbevole dosis</i>
Tussen 30 en 60 ml/min	2 mg per dag
Tussen 15 en 30 ml/min	2 mg elke tweede dag
Minder as 15 ml/min	2 mg op die dag van die dialise*

*Die gemiddelde dialise-opruiming van perindopriël is 52 ml/minuut en dié van perindopriëel, 67,2 ml/minuut.

NEWE-EFFEKTE EN SPESIALE VOORSORGMATREËLS

Neuwe-effekte

Die onderstaande ongewenste reaksies is waargeneem gedurende behandeling met **PEARINDA** en word volgens die onderstaande frekwensies geklassifiseer:

Baie algemeen ($\geq 1/10$); algemeen ($\geq 1/100$, $< 1/10$); ongewoon ($\geq 1/1000$, $< 1/100$); seldsaam ($\geq 1/10000$, $< 1/1000$); baie seldsaam ($< 1/10000$), insluitende geïsoleerde aanmeldings.

Hematologiese versteurings

Baie seldsaam: Afnames in witbloedseltelling, hemoglobien en hematokrit, beenmurgonderdrukking, anemie, trombositopenie, agranulositose, hemolitiese anemie.

Kardiovaskulêre versteurings

Dikwels: Ortostatiese reaksies, insluitende hipotensie..
Baie seldsaam: Miokardiale infarsie, serebrovaskulêre ongeval, palpitasies, tagikardie, borspyn.

Neurologiese versteurings

Algemeen: Duiseligheid, hoofpyn, parestesie, vertigo, vermoeidheid.
Ongewoon: Gemoedsveranderinge, slaapversteurings.
Baie seldsaam: Verstandelike verwardheid.

Endokriene/Metaboliese versteurings

Baie seldsaam: Hiperkalemie, hiponatremie, toenames in bloedureum en toenames in serumkreatinien.

Gastroïntestinale versteurings

Algemeen: Diarree, naarheid, abdominale pyn, indigestie, braking, smaakversteurings, hardlywigheid.

Ongewoon: Droë mond.

Baie seldsaam: Pankreatitis.

Nier-/Genito-urinêre versteurings

Ongewoon: Impotensie.

Baie seldsaam: Uremie, oligurie, anurie, nierdisfunksie, akute nierversaking.

Lewer-/hepatiese

Seldsaam: Geelsug, toenames in lewerensieme, toenames in serumbilirubien.

Baie seldsaam: Hepatitis (hepatosellulêr of cholestaties).

Muskuloskeletale versteurings

Algemeen: Astenie, spierkrampe.

Respiratoriese versteurings

Algemeen: Hoes, dispnee.

Ongewoon: Brongospasma.

Baie seldsaam: Rinitis, sinusitis, eosinofilliese pneumonie.

Velversteurings

Algemeen: Uitslag, pruritus.

Ongewoon: Urtikarie, sweet.

Baie seldsaam: Diaforese, alopesie, psoriase, erge velaandoenings insluitende pemfigus, toksiese epidermale nekrolise, Stevens-Johnson-sindroom en veelvuldige eriteem. Veluitslag, fotosensitiwiteit of ander dermatologiese manifestasies kan moontlik voorkom.

Ander

Algemeen: Sigstoornis, tinnitus.

Ongewoon: Hipersensitiwiteit/angio-edeem-reaksies: angio-edeem van die gesig, ekstremiteite, lippe, tong, glottis en/of larinks, wat noodlottig kan wees.

Seldsaam: Intestinale angio-edeem.

Baie seldsaam: 'n Simptoomkompleks is aangemeld wat kan insluit: koors, vaskulitis, mialgie, artritis/artralgie, 'n positiewe antinuklêre teenliggaam (ANA), verhoogde eritrosietbesinkingspoed, eosinofilie en leukositose.

Spesiale voorsorgmaatreëls:

- Miokardiale infarsie en serebrovaskulêre ongevallen kan voorkom weens erge verlaging van bloeddruk by hoë-risikopasiënte, bv. diene met iskemiese hartsiekte of serebrovaskulêre siekte.
- By pasiënte met volume-uitputting of pasiënte met iskemiese hartsiekte of serebrovaskulêre siekte moet behandeling gemonitor word, veral as die **PEARINDA** of diuretikum dosis aangepas word.
- Indien hipotensie voorkom, moet die pasiënt op die rug neergelê word en, indien nodig, 'n intraveneuse infusie van 0,9%-soutoplossing ontvang.
- Toenames in bloedureum en serumkreatinien is waargeneem by pasiënte met geen opsigtelike voorafbestaande vaskulêre siekte nie, veral wanneer **PEARINDA** saam met 'n diuretikum gegee word. Vermindering van die dosis of staking van **PEARINDA** of die diuretikum kan nodig wees.
- Tekens van swelling van die gesig of ekstremitate of probleme om te sluk of om asem te haal, vereis onmiddellike mediese aandag, weens die risiko van angioedeem. **PEARINDA** moet gestaak word. Sodanige pasiënt moet nooit weer enige **PEARINDA**, AOE-remmers of angiotensien-reseptor-blokkers ontvang nie.
- Omsigtigheid word aangeraai wanneer 'n voertuig bestuur word of take uitgevoer word wat wakkerheid vereis aangesien duiseligheid kan voorkom.
- By pasiënte wat ernstige chirurgie ondergaan of tydens narkose met middels wat hipotensie veroorsaak, kan **PEARINDA** angiotensien II-vorming blokkeer sekondêr tot aanvullende renienvrystelling. Indien hipotensie voorkom wat aan hierdie meganisme toegeskryf kan word, kan dit deur volume-aanvulling reggestel word.
- Verswakte nierfunksie – verlaagde eliminasië van **PEARINDA** wat lei tot 'n verhoogde risiko van hiperkalemie. Hierdie pasiënte kan laer dosisse benodig.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN

(Sien "**NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREËLS**")

Simptome van oordosering

Erge hipotensie, elektrolietversteurings en nierversaking.

Behandeling van oordosis

Behandeling is simptome en ondersteunend. Geaktiveerde houtskool kan tydens erge oordosering gegee word indien die pasiënt binne 1 uur ná inname aanmeld.

Behandeling bestaan uit volume-aanvulling om hipotensie reg te stel en behandeling

van dehidrasie en elektrolietwanbalans. **PEARINDA** is verwyderbaar deur hemodialise.

IDENTIFIKASIE

PEARINDA 4: 'n Wit kapsulevormige tablet met afmetings van ongeveer 8 x 4 mm, met 'n breeklyn aan albei kante

PEARINDA 8: 'n Wit ronde konvekse tablet, met 'n deursnee van ongeveer 8 mm met 'n breeklyn aan een kant.

AANBIEDING

PEARINDA 4: Die tablette is beskikbaar in PA-Alu-PVC/Alu-stolpverpakking van 30's.

PEARINDA 8: Die tablette is beskikbaar in PA-Alu-PVC/Alu-stolpverpakking van 30's.

BERGINGSAAWYSINGS

Bewaar benede 25 °C.

Hou die stulpverpakkings in die karton tot benodig vir gebruik.

HOU BUIE DIE BEREIK VAN KINDERS.

REGISTRASIENOMMERS

PEARINDA 4: 41/7.1.3/0649

PEARINDA 8: 41/7.1.3/0650

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT:

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