PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

RAN-PERINDOPRIL 4 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains perindopril tert-butylamine 4 mg.

Contains sugar: Lactose monohydrate 29,192 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White to off-white, capsule shaped tablets debossed with ‘P’ & ‘5’ on either side of the score line on one side and a deep break line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RAN-PERINDOPRIL 4 tablets are indicated for the:

- Treatment of mild to moderate hypertension.
- Treatment of congestive heart failure not adequately controlled by conventional therapy with diuretics and digitalis and in whom vasodilatation is indicated.
- Reduction of risk of cardiac events in patients with stable coronary artery disease and without heart failure.

4.2 Posology and method of administration

Posology

Mild to moderate hypertension

Adults: The initial dose is 4 mg taken in the morning before breakfast which can be increased to a single dose of 8 mg according to the blood pressure response. The full therapeutic effect may take several weeks. Therefore, if the desired effect has not been achieved within a month of treatment, the dose may be increased.

Congestive heart failure

The treatment should be initiated under close medical supervision. The initial dose is 2 mg orally as a single dose in the morning which may, in most cases, be increased to 4 mg (once blood pressure acceptability has been demonstrated).

Special populations

Reduction of risk of cardiovascular events

In patients with stable coronary artery disease, RAN-PERINDOPRIL 4 should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function.

Elderly population

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see table below).

Dosing in high-risk individuals

Diuretic-treated patients: In order to minimise the possibility of sudden and severe hypotension which may occur within the first 1 to 5 hours after the initial dose of RAN-PERINDOPRIL 4, diuretics should be discontinued for two to three days before beginning therapy with RAN-PERINDOPRIL 4. In patients where diuretic therapy cannot be discontinued, it is recommended that a potassium salt or a potassium sparing agent not be prescribed.

Renal impairment

In patients with renal insufficiency, the dose of RAN-PERINDOPRIL 4 must be adjusted according to the severity of the insufficiency.

The following dosage is recommended:

Creatinine clearance	**Recommended dosage**
Between 30 and 60 mL/min	2 mg per day

Perindopril is dialysable (70 mL/min).

For patients on haemodialysis, the dose should be taken after dialysis.

Hepatic impairment

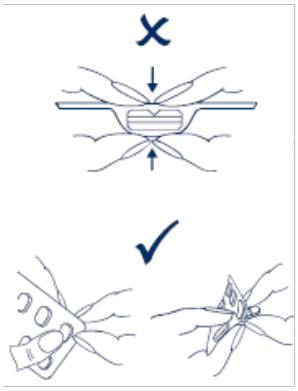
No dosage adjustment is necessary in patients with hepatic impairment.

Method of administration

RAN-PERINDOPRIL 4 must be taken in the morning before breakfast.

To remove the tablet intact from the blister, gently push down the tablet from the top to the bottom foil and peel off the aluminium foil.

See below picture for guidance:



4.3 Contraindications

- Hypersensitivity to perindopril or to any of the excipients listed in section 6.1.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.

- Lithium therapy: Concomitant administration with RAN-PERINDOPRIL 4 may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of RAN-PERINDOPRIL 4 with aliskiren-containing products is contraindicated (see section 4.4 and section 4.5).
- Concomitant use of fluoroquinolones with RAN-PERINDOPRIL 4 is contraindicated in patients with moderate to severe renal impairment.
- Concomitant use of sacubitril/valsartan (see section 4.5).
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving RAN-PERINDOPRIL 4, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and section 4.6).

Stable coronary artery disease

If an episode of unstable angina pectoris (major or not) occurs during the first month of RAN-PERINDOPRIL 4 treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension

RAN-PERINDOPRIL 4 may cause a fall in blood pressure. Symptomatic hypotension is seen less frequently in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see section 4.5). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an

excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of 0,9 % sodium chloride. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty once the blood pressure has increased after volume expansion. In patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with RAN-PERINDOPRIL 4. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of RAN-PERINDOPRIL 4 may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

RAN-PERINDOPRIL 4 should not be given to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy (see section 4.3).

Renal impairment

In cases of renal impairment (creatinine clearance < 60 mL/min), the initial RAN-PERINDOPRIL 4 dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and thereafter as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see section 4.3).

In patients with symptomatic heart failure, hypotension following the initiation of therapy with RAN-PERINDOPRIL 4 may lead to further impairment in renal function. In this situation acute renal failure, usually reversible, has been reported.

In patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with RAN-PERINDOPRIL 4, increases in blood urea and serum creatinine, which may be reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency (see section 4.3).

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, especially when RAN-PERINDOPRIL 4 has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or RAN-PERINDOPRIL 4 may be required.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE inhibitor, such as RAN-PERINDOPRIL 4. In these patients, consideration should be given to using a different type of dialysis membrane or different class of antihypertensive medicine.

Kidney transplantation

There is no experience regarding the administration of RAN-PERINDOPRIL 4 in patients with a recent kidney transplantation.

Hypersensitivity/angioedema

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including RAN-PERINDOPRIL 4 (see section 4.3 and section 4.8). This may occur at any time during therapy. In such cases, RAN-PERINDOPRIL 4 should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of epinephrine (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.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving RAN-PERINDOPRIL 4 (see section 4.3).

Intestinal angioedema has been reported less frequently 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. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors, such as RAN-PERINDOPRIL 4 presenting with abdominal pain.

Anaphylactoid reactions during low-density lipoproteins LDL apheresis

Less frequently, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation

Patients receiving ACE inhibitors such as RAN-PERINDOPRIL 4 during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In these patients, such reactions may be avoided when the ACE inhibitors are temporarily suspended. However, these reactions may reappear upon inadvertent rechallenge.

Hepatic failure

ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving RAN-PERINDOPRIL 4 who develop jaundice or marked elevations of hepatic enzymes should discontinue the RAN-PERINDOPRIL 4 and receive appropriate medical follow-up (see section 4.8).

Neutropenia/agranulocytosis/thrombocytopenia/anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, such as RAN-PERINDOPRIL 4. In patients with normal renal function and no other complicating factors, neutropenia occurs less frequently. RAN-PERINDOPRIL 4 should be used with extreme 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. Patients may develop serious infections. If RAN-PERINDOPRIL 4 is used in these patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Race

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

RAN-PERINDOPRIL 4 may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors, such as RAN-PERINDOPRIL 4. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/anaesthesia

In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, RAN-PERINDOPRIL 4 may block angiotensin II formation secondary to compensatory renin release. The treatment 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.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including RAN-PERINDOPRIL 4. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, inter-current events, in particular dehydration, acute cardiac decompensation, metabolic acidosis or those using concomitant potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increases in serum potassium. Hyperkalaemia can cause serious, sometimes fatal dysrhythmias (see section 4.5 and section 4.3).

Diabetic patients

In diabetic patients treated with oral antidiabetic medicines or insulin, glycaemic control should be closely monitored during the first month of treatment with RAN-PERINDOPRIL 4 (see section 4.5).

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 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 RAN-PERINDOPRIL 4 and aliskiren is therefore contraindicated (see section 4.3).

RAN-PERINDOPRIL 4 should not be used concomitantly with aliskiren (see section 4.3).

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 sections 4.3 and 4.5)

Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE-inhibitors may also increase the risk of angioedema (see section 4.5). Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus:

Patients taking concomitant mTOR inhibitors (e.g sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment. (see section 4.3)

Lithium

The combination of lithium and RAN-PERINDOPRIL 4 is generally not recommended (see section 4.5).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

The combination of RAN-PERINDOPRIL 4 and potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended (see section 4.5).

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 of RAN-PERINDOPRIL 4 is not recommended.

Concomitant use of fluoroquinolones:

Concomitant use of fluoroquinolones and RAN-PERINDOPRIL 4 may precipitate acute kidney injury (AK) in patients, especially those with moderate to severe renal failure and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment, with concomitant use of fluoroquinolones and RAN-PERINDOPRIL 4 (see sections 4.3 and 4.5).

Excipients

RAN-PERINDOPRIL 4 contains lactose monohydrate 29,192 mg per tablet. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Medicines inducing hyperkalaemia

Some medicines or therapeutic classes may increase the occurrence of hyperkalaemia: potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim. The combination with these medicines increases the risk of hyperkalaemia.

Concomitant use contraindicated (see section 4.3)

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

Clinical trial data has 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 section 4.3, and section 4.4).

Estramustine

Risk of increased adverse effects such as angioedema.

Potassium-sparing diuretics (e.g. triamterene, amiloride), potassium salts

Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects).

Lithium

Increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors such as RAN-PERINDOPRIL 4. Use of RAN-PERINDOPRIL 4 with lithium is contraindicated (see section 4.3).

Aliskiren

In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality may increase.

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. polyacrylonitrile membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Sacubitril/Valsartan

The concomitant use of perindopril with sacubitril/valsartan is contra-indicated as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be

started until 36 hours after the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.3)

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers

Concomitant use of fluoroquinolones and RAN-PERINDOPRIL 4 may precipitate acute kidney injury (see sections 4.3 and 4.4). It has been reported that AKI occurred soon after ciprofloxacin was prescribed in patients taking enalapril. The interaction between ACE-inhibitors and fluoroquinolones to precipitate AKI is a class effect for all ACE-inhibitors and not just enalapril and also a class effect of all fluoroquinolones, not just with ciprofloxacin.

Concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker:

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with 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.

Co-trimoxazole (trimethoprim/sulphamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/ sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.3).

Concomitant use which requires special care

Antidiabetic agents (insulins, oral hypoglycaemic agents)

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Baclofen

Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

Non-potassium-sparing diuretics

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with RAN-PERINDOPRIL 4. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of RAN-PERINDOPRIL 4.

In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating RAN-PERINDOPRIL 4, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or RAN-PERINDOPRIL 4 must be initiated with a low dosage and progressively increased.

In diuretic-treated congestive heart failure, RAN-PERINDOPRIL 4 should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of RAN-PERINDOPRIL 4 therapy.

Potassium-sparing diuretics (eplerenone, spironolactone)

With eplerenone or spironolactone at doses between 12,5 mg to 50 mg by day and with low doses of ACE-inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40 %, and previously treated with ACE-inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.

Before initiating the combination, check the absence of hyperkalaemia and renal impairment.

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

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

When RAN-PERINDOPRIL 4 is administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of RAN-PERINDOPRIL 4 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.

Racecadotril

ACE-inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a medicine used against acute diarrhoea).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

Concomitant use which requires some care

Antihypertensive medicines and vasodilators

Concomitant use of these medicines may increase the hypotensive effects of RAN-PERINDOPRIL 4. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Gliptins (saxagliptin, vildagliptin)

Increased risk of angioedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptin, in patients co-treated with an ACE inhibitor such as RAN-PERINDOPRIL 4.

Tricyclic antidepressants/antipsychotics/anaesthetics

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE inhibitors such as RAN-PERINDOPRIL 4 may result in further reduction of blood pressure (see section 4.4).

Acetylsalicylic acid, thrombolytics, beta-blocker and nitrates

RAN-PERINDOPRIL 4 may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of RAN-PERINDOPRIL 4.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported less frequently in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including RAN-PERINDOPRIL 4.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of RAN-PERINDOPRIL 4 is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take RAN-PERINDOPRIL 4 during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with RAN-PERINDOPRIL 4 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 spins bifida) and of kidney malformations.

RAN-PERINDOPRIL 4 passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of RAN-PERINDOPRIL 4 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).

Infants who have been exposed *in utero* to RAN-PERINDOPRIL 4 should be closely monitored.

Peritoneal dialysis may be of some benefit in the clearance of RAN-PERINDOPRIL 4 from the neonatal circulation.

Breastfeeding

Safety in lactation has not been established (see section 4.3).

4.7 Effects on ability to drive and use machines

RAN-PERINDOPRIL 4 has no direct influence on the ability to drive and use machines, 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. As a result, the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA System organ	Frequency	Adverse reactions

class		
Blood and lymphatic system disorders	Less frequent	Decreases in haemoglobin and haematocrit, thrombocytopenia, leukopenia/neutropenia, agranulocytosis or pancytopenia, eosinophilia, haemolytic anaemia.
Immune system disorders	Less frequent	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx.
Metabolism and nutrition disorders	Less frequent	Hyperkalaemia, hyponatraemia, hypoglycaemia.
Psychiatric disorders	Less frequent	Mood disturbances, sleep disorder.
Nervous system disorders	Frequent	Dizziness, headache, paraesthesia, vertigo.
	Less frequent	Somnolence, syncope, confusion.
Eye disorders	Frequent	Visual disturbances.
Ear and labyrinth disorders	Frequent	Tinnitus.
Cardiac disorders	Less frequent	Palpitations, tachycardia, angina pectoris, dysrhythmia, myocardial infarction (see section 4.4).
Vascular disorders	Frequent	Hypotension.
	Less frequent	Vasculitis, stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, dyspnoea.
	Less frequent	Bronchospasm, rhinitis, eosinophilic pneumonia.
Gastrointestinal disorders	Frequent	Diarrhoea, abdominal pain, constipation, dysgeusia, dyspepsia, nausea, vomiting.
	Less frequent	Dry mouth, pancreatitis.

Hepatobiliary disorders	Less frequent	Hepatitis either cytolytic or cholestatic.
Skin and subcutaneous tissue disorders	Frequent	Pruritus, rash.
	Less frequent	Urticaria, photosensitivity reactions, pemphigoid, hyperhidrosis, erythema multiforme; psoriasis aggravation.
Musculoskeletal and connective tissue disorders	Frequent	Muscle cramps.
	Less frequent	Arthralgia, myalgia
Renal and urinary disorders	Less frequent	Renal insufficiency, acute renal failure.
Reproductive system and breast disorders	Less frequent	Erectile dysfunction.
General disorders and administration site conditions	Frequent	Asthenia.
	Less frequent	Chest pain, malaise, peripheral oedema, pyrexia, sweating.
Investigations	Less frequent	Increased blood urea, increased blood creatinine, increased blood bilirubin, increased hepatic enzymes.
Injury, poisoning and procedural complications	Less frequent	Fall.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

See section 4.8.

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 overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume expansion to correct hypotension and treating dehydration and electrolyte imbalances. RAN-PERINDOPRIL 4 is removable by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class & category: A 7.1.3 Other hypotensives

Perindopril inhibits angiotensin I-converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels result 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.

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity *in vitro*.

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.

5.2 Pharmacokinetic properties

Absorption

Perindopril is well absorbed after oral administration (peak concentration within 1 hour) with wide variability between patients. The plasma half-life of perindopril is equal to 1 hour.

The bioavailability of perindoprilat, the active metabolite, is 27 %.

The time to achieve peak serum concentration of perindoprilat, the active metabolite, is within 3 to 4 hours and peak pharmacological activity is obtained within 4 to 6 hours.

The ingestion of food decreases conversion to perindoprilat, and hence bioavailability. Therefore, perindopril should be administered orally in a single daily dose in the morning before breakfast.

Distribution

The volume of distribution is approximately 0,2 L/kg for unbound perindoprilat. Protein binding is slight (binding of perindoprilat to plasma proteins is 20 %, principally to angiotensin converting enzyme), but is concentration-dependent.

Biotransformation

Apart from the active perindoprilat, perindopril gives rise to 5 other metabolites, all of which are inactive.

Elimination

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Colloidal anhydrous silica
- Lactose monohydrate
- Magnesium stearate
- Microcrystalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C in the original package, protected from moisture.

6.5 Nature and contents of container

Cartons contain 30 tablets packed in cold form blister strips of 10 tablets each. Cold form blister strips comprise of cold form blister laminate composed of aluminium foil (one side bright, soft tempered, plain; dull side lacquer laminated to oriented polyamide film; bright side lacquer laminated to PVC film), PVC and polyamide with a backing of aluminium foil coated with heat seal lacquer on the inner side.
Alternatively, 10 tablets are packed in PVC blister strips in triple laminated aluminium pouch comprised of clear PVC film with the backing of aluminium foil coated with heat sealed lacquer on inner side. Three such PVC blisters are further packed in a triple laminated aluminium pouch with desiccant and sealed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1, Roodepoort

Johannesburg,

1724.

8. REGISTRATION NUMBER:

42/7.1.3/0107

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 April 2008

10. DATE OF REVISION OF THE TEXT

25 February 2022

Botswana: S2 Reg. no.: BOT0801268

Namibia: NS2 Reg. no.: 20/7.1.3/0348

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS: S3

1. NAAM VAN DIE MEDISYNE

RAN-PERINDOPRIL 4 Tablette

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

Elke tablet bevat 4 mg perindopril tert-butielamien.

Bevat suiker: 29,192 mg Laktosemonohidraat.

Vir die volledige lys van onaktiewe bestanddele, sien afdeling 6.1.

3. FARMASEUTIESE VORM

Tablette

Wit tot naaswit, kapsule-vormige tablette ingestempel met ‘P’ & ‘5’ op enige kant van die keeplyn op die een kant en ‘n diep breeklyn op die ander kant.

4. KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

RAN-PERINDOPRIL 4 tablette word aangedui vir die:

- Behandeling van ligte tot matige hipertensie.
- Behandeling van kongestiewe hartversaking wat nie voldoende deur konvensionele terapie met diuretika en digitalis beheer word nie en by wie vasodilatasie aangedui is.
- Vermindering van die risiko van kardiale voorvalle by pasiënte met stabiele koronêre vatsiekte en sonder hartversaking.

4.2 Posologie en metode van toediening

Posologie

Ligte tot matige hipertensie

Volwassenes: Die aanvanklike dosis is 4 mg in die oggend voor ontbyt geneem wat tot ‘n enkeldosis van 8 mg verhoog kan word volgens die bloeddrukrespons. Die volle terapeutiese effek kan verskeie weke neem. Daarom, as die gewenste effek nie binne ‘n maand van behandeling bereik word nie, kan die dosis verhoog word.

Kongestiewe hartversaking

Die behandeling moet onder streng mediese toesig geïnisieer word. Die aanvanklike dosis is 2 mg oraal geneem as ‘n enkeldosis in die oggend wat, in die meeste gevalle, verhoog kan word na 4 mg (sodra aanvaarbare bloeddruk aangetoon is).

Spesiale populasies

Vermindering van die risiko van kardiovaskulêre voorvalle

By pasiënte met stabiele koronêre arterie-siekte, moet RAN-PERINDOPRIL 4 teen ‘n dosis van 4 mg een keer per dag vir twee weke toegedien word, dan verhoog word na 8 mg een keer per dag, afhangende van die nierfunksie.

Bejaarde populasie

Bejaarde pasiënte moet 2 mg een keer per dag vir een week ontvang, dan 4 mg een keer per dag vir die volgende week, voordat die dosis verhoog moet word tot by 8 mg een keer per dag afhangende van die nierfunksie (sien tabel hieronder).

Dosering by hoë-risiko individue

Diureties-behandelde pasiënte: Ten einde die moontlikheid van skielike en ernstige hipotensie te minimaliseer wat mag voorkom binne die eerste 1 tot 5 uur na die aanvanklike dosis van RAN-PERINDOPRIL 4**,** moet diuretika onttrek word vir twee tot drie dae voordat met RAN-PERINDOPRIL 4 terapie begin word. By pasiënte waar diuretiese terapie nie onttrek kan word nie, word dit aanbeveel dat ‘n kaliumsout of ‘n kaliumsparende middel nie voorgeskryf word nie.

Nierinkorting

By pasiënte met nierinkorting, moet die dosis van RAN-PERINDOPRIL 4 aangepas word volgens die ernstigheid van die inkorting.

Die volgende dosis word aanbeveel:

Kreatinienopruiming	**Aanbevole dosis**
Tussen 30 en 60 mL/min	2 mg per dag

Perindopril is dialiseerbaar (70 mL/min).

Vir pasiënte op hemodialise, moet die dosis na dialise geneem word.

Lewerinkorting

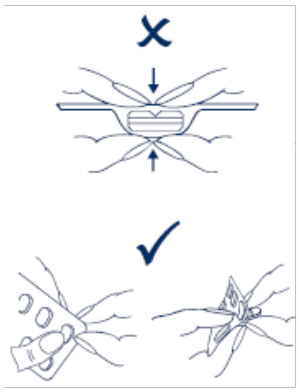
Geen dosisaanpassing is nodig by pasiënte met lewerinkorting nie.

Metode van toediening

RAN-PERINDOPRIL 4 moet in die oggend voor ontbyt geneem word.

Om die tablet intakt uit die stulpverpakking te verwyder, druk die tablet liggies van die boonste na die onderste foelie en trek die aluminiumfoelie af.

Sien onderstaande prentjie vir leiding:



4.3 Kontraindikasies

- Hipersensitiwiteit teenoor perindopril of enige van die onaktiewe bestanddele gelys in afdeling 6.1.
- ‘n Geskiedenis van angio-edeem verwant aan vorige terapie met AOE-remmers of angiotensien-reseptorblokkeermiddels (ARBs). Hierdie pasiënte moet nooit weer hierdie medisyne ontvang nie.
- Oorerflike of idiopatiese angio-edeem.
- Hipertrofiese obstruktiewe kardiomiopatie (HOKM).
- Ernstige inkorting van nierfunksie (kreatinienopruiming minder as 30 mL/min).
- Bilaterale renale arterie stenose.
- Renale arterie stenose by pasiënte met ‘n enkele nier.
- Aortiese stenose.
- Gelyktydige terapie met kaliumsparende diuretika soos spironolaktoon, triamtereen, amiloried (sien afdeling 4.5).

- Porfirie.
- Litiumterapie: Gelyktydige toediening met RAN-PERINDOPRIL 4 kan lei tot toksiese bloedvlakke van litium (sien afdeling 4.5).
- Swangerskap en laktasie (sien afdeling 4.6).
- Die gelyktydige gebruik van RAN-PERINDOPRIL 4 met aliskiren-bevattende produkte is teenaangedui (sien afdeling 4.4 en afdeling 4.5).
- Gelyktydige gebruik van fluorokinolone met RAN-PERINDOPRIL 4 is teenaangedui by pasiënte met matige tot ernstige nierinkorting.
- Gelyktydige gebruik van sakubitriel/valsartan (sien afdeling 4.5).
- Ekstrakorporeale behandelings wat lei tot kontak van bloed met negatief-gelaaide oppervlakke (sien afdeling 4.5)

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Indien ‘n vrou swanger sou raak terwyl sy RAN-PERINDOPRIL 4 ontvang**,** moet die behandeling dadelik gestaak word en oorgeskakel word na ‘n ander klas van antihipertensiewe medisyne (sien afdeling 4.3 en afdeling 4.6).

Stabiele koronêre vatsiekte

As ‘n episode van onstabiele angina pectoris (major of nie) gedurende die eerste maand van behandeling met RAN-PERINDOPRIL 4 voorkom, moet noukeurige bepaling van die voordeel/risiko gedoen word voordat behandeling kan voortgaan.

Hipotensie

RAN-PERINDOPRIL 4 kan ‘n daling in bloeddruk veroorsaak. Simptomatiese hipotensie is minder dikwels waargeneem in ongekompliseerde hipertensiewe pasiënte en sal meer waarskynlik voorkom by pasiënte wat volume-uitgeput is bv. deur diuretiese terapie, dieetsoutbeperking, dialise, diaree of braking, of wat erge renien-afhanklike hipertensie het (sien afdeling 4.5). By pasiënte met simptomatiese hartversaking, met of sonder geassosieerde nierinkorting, is simptomatiese hipotensie waargeneem. Die voorkoms is meer waarskynlik by daardie pasiënte met meer ernstige grade van hartversaking, soos gereflekteer deur die gebruik van hoë dosisse lusdiuretika, hiponatremie of funksionele nierinkorting. By pasiënte met verhoogde risiko van simptomatiese hipotensie, moet

inisiëring van terapie en dosisaanpassing noukeurig gemoniteer word. Soortgelyke oorwegings is van toepassing op pasiënte met iskemiese hart- of serebrovaskulêre siekte by wie 'n oormatige val in bloeddruk 'n miokardiale infarksie of serbrovaskulêre voorval as resultaat kan hê. As hipotensie voorkom, moet die pasiënt in die rugliggende posisie geplaas word en, as nodig, 'n intraveneuse infusie van 0,9 % natriumchloried ontvang. 'n Verbygaande hipotensiewe respons is nie teenaangedui vir verdere dosisse nie wat gewoonlik sonder moeite toegedien kan word sodra die bloeddruk verhoog het na volume uitsetting. By pasiënte met kongestiewe hartversaking wat normale of lae bloeddruk het, kan bykomende verlaging van die sistemiese bloeddruk voorkom met RAN-PERINDOPRIL 4. Hierdie effek word verwag en is gewoonlik nie die rede om behandeling te staak nie. As hipotensie simptomaties raak, kan 'n verlaging van die dosis of staking van RAN-PERINDOPRIL 4 nodig wees.

Aortiese en mitraalklepstenose/hipertrofiese kardiomiopatie

RAN-PERINDOPRIL 4 moet nie aan pasiënte met mitraalklepstenose gegee word nie en by obstruksie van die uitvloei vanuit die linker ventrikel soos vir aortiese stenose of hipertrofiese kardiomiopatie (sien afdeling 4.3).

Nierinkorting

In gevalle van nierinkorting (kreatinienopruiming < 60 mL/min), moet die aanvanklike RAN-PERINDOPRIL 4 dosis aangepas word volgens die pasiënt se kreatinienopruiming (sien afdeling 4.2) en daarna as 'n funksie van die pasiënt se respons op behandeling. Roetine monitering van kalium en kreatinien is deel van normale mediese praktyk vir hierdie pasiënte (sien afdeling 4.3).

By pasiënte met simptomatiese hartversaking, kan hipotensie as gevolg van die inisiëring van terapie met RAN-PERINDOPRIL 4 lei tot verdere inkorting van die nierfunksie. In hierdie geval word akute nierversaking, gewoonlik omkeerbaar, aangemeld.

By pasiënte met bilaterale renale arterie stenose of stenose van die arterie van 'n enkele nier, wat met RAN-PERINDOPRIL 4 behandel is, is verhogings in bloedureum en serumkreatinien waargeneem, wat omkeerbaar mag wees met staking van terapie. Dit is veral waarskynlik by pasiënte met nierinkorting. As renovaskulêre hipertensie ook teenwoordig is, is daar 'n verhoogde risiko van ernstige hipotensie en nierontoereikendheid (sien afdeling 4.3).

Sommige hipertensiewe pasiënte, met geen oënskynlike voorafbestaande renale vaskulêre siekte, het verhogings in bloedureum en serumkreatinien ontwikkel, veral wanneer RAN-PERINDOPRIL 4 gelyktydig met 'n diuretikum toegedien is. Dit is meer waarskynlik om voor te kom by pasiënte met

voorafbestaande nierinkorting. Dosisverlaging en/of onttrekking van die diuretikum en/of RAN-PERINDOPRIL 4 mag nodig wees.

Hemodialise pasiënte

Anafilaktoïede reaksies is aangemeld by pasiënte wat met hoë vloeimembrane gedialiseer word, en gelyktydig met ‘n AOE-remmer, soos RAN-PERINDOPRIL 4**.** By hierdie pasiënte moet oorweging daaraan geskenk word om ‘n verskillende tipe van dialise-membraan of verskillende klas van antihipertensiewe medisyne te gebruik.

Nieroorplanting

Daar is geen ondervinding aangaande die toediening van RAN-PERINDOPRIL 4 by pasiënte met ‘n onlangse nieroorplanting nie.

Hipersensitiwiteit/angio-edeem

Angio-edeem van die gesig, ekstremiteite, lippe, slymvliesmembrane, tong, glottis en/of larinks is aangemeld by pasiënte wat met AOE-remmers behandel is, insluitende RAN-PERINDOPRIL 4 (sien afdeling 4.3 en afdeling 4.8). Dit kan op enige tydstip tydens behandeling voorkom. In sulke gevalle moet, RAN-PERINDOPRIL 4 dadelik onttrek word en behoorlike monitering moet ingestel word en volgehou word totdat volledige opklaring van simptome plaasgevind het.

Angio-edeem geassosieer met laringeale edeem kan fataal wees. Waar daar betrokkenheid van die tong, glottis of larinks is, wat waarskynlik die oorsaak van lugwegobstruksie is, moet noodbehandeling onmiddellik toegepas word. Dit kan die toediening van epinefrien (adrenalien) en/of die instandhouding van ‘n sigbare lugweg insluit. Die pasiënt moet onder noukeurige mediese toesig wees totdat volledige en volgehoue opklaring van simptome plaasgevind het.

Pasiënte met ‘n geskiedenis van angio-edeem wat nie verwant is aan AOE-remmer terapie nie, kan ‘n verhoogde risiko van angio-edeem hê terwyl hulle RAN-PERINDOPRIL 4 ontvang (sien afdeling 4.3).

Intestinale angio-edeem is minder dikwels aangemeld by pasiënte wat met AOE-remmers behandel is. Hierdie pasiënte presenteer met abdominale pyn (met of sonder naarheid of braking); in sommige gevalle was daar geen vooraf gesigsangio-edeem nie en C-1 esterase-vlakke was normaal. Intestinale angio-edeem moet ingesluit word in die onderskeie diagnoses van pasiënte op AOE-remmers, soos RAN-PERINDOPRIL 4 wat met abdominale pyn presenteer.

Anafilaktoïede reaksies tydens lae-digtheid lipoproteïen LDL-aferese

Pasiënte wat AOE-remmers tydens lae-digtheid lipoproteïen (LDL)-aferese met dekstraansulfaat ontvang het, het minder dikwels lewensbedreigende anafilaktoïede reaksies ervaar. Hierdie reaksies is vermy deur tydelike terughouding van terapie met ‘n AOE-remmer voor elke aferese.

Anafilaktiese reaksies tydens desensitisasie

Pasiënte wat AOE-remmers soos RAN-PERINDOPRIL 4 tydens desensitiseringsbehandeling ontvang (bv. himenoptera gifstof), het anafilaktoïede reaksies ervaar. By hierdie pasiënte, kan sulke reaksies vermy word wanneer die AOE-remmers tydelik opgeskort word. Hierdie reaksies kan egter weer opduik met onbewustelike heruitdaging.

Lewerversaking

AOE-remmers word geassosieer met ‘n sindroom wat begin met cholestatiese geelsug en vorder tot skielike en ernstige hepatiese nekrose en (somtyds) sterfte. Die meganisme van hierdie sindroom word nie verstaan nie. Pasiënte wat RAN-PERINDOPRIL 4 ontvang wat geelsug of merkbare verhogings van hepatiese ensieme ontwikkel, moet die RAN-PERINDOPRIL 4 staak en behoorlik medies opgevolg word (sien afdeling 4.8).

Neutropenie/agranulositose/trombositopenie/anemie

Neutropenie/agranulositose, trombositopenie en anemie is aangemeld by pasiënte wat AOE-inhibeerders, soos RAN-PERINDOPRIL 4 ontvang het**.** By pasiënte met normale nierfunksie en geen ander kompliserende faktore, het neutropenie minder dikwels voorgekom. RAN-PERINDOPRIL 4 moet met uiterste sorg gebruik word by pasiënte met kollageen vaskulêre siekte, immuunonderdrukkende terapie, behandeling met allopurinol of prokaïenamied, of ‘n kombinasie van hierdie kompliserende faktore, veral as daar voorafbestaande ingekorte nierfunksie is. Pasiënte kan ernstige infeksies ontwikkel.

As RAN-PERINDOPRIL 4 by hierdie pasiënte gebruik word, word die periodieke monitering van witbloedseltelling aangeraai en pasiënte moet in kennis gestel word om enige tekens van infeksie (bv. seerkeel, koors) aan te meld.

Ras

AOE-remmers veroorsaak ‘n hoër mate van angio-edeem in swart pasiënte as in nie-swart pasiënte. RAN-PERINDOPRIL 4 kan minder effektief wees om die bloeddruk te verlaag in swart persone as in

nie-swart persone, moontlik as gevolg van 'n aangemelde hoër voorkoms van lae-renien toestande in die swart hipertensiewe populasie.

Hoes

Hoes is aangemeld met die gebruik van AOE-remmers, soos RAN-PERINDOPRIL 4. Kenmerkend is die hoes onproduktief, aanhoudend en klaar op na staking van terapie. AOE-remmer-geïnduseerde hoes moet oorweeg word as deel van die differensiële diagnose van hoes.

Chirurgie/narkose:

By pasiënte wat major chirurgie ondergaan of tydens narkose met medisyne wat hipotensie veroorsaak, kan RAN-PERINDOPRIL 4 angiotensien-II vorming sekondêr tot kompenserende renienvrystelling blokkeer. Die behandeling moet een dag voor die chirurgie gestaak word. Indien hipotensie voorkom en van mening is dat dit as gevolg van hierdie meganisme is, kan dit reggestel word deur toename in volume.

Hiperkalemie

Verhogings in serum kaliumvlakke het voorgekom by sommige pasiënte wat met AOE-remmers, insluitende RAN-PERINDOPRIL 4**,** behandel is. Pasiënte met die risiko om hiperkalemie te ontwikkel, insluitende die met nierinkorting, verslegting van die nierfunksie, ouderdom (>70 jaar), diabetes mellitus, lopende voorvalle, veral dehidrasie, akute kardiale dekompensasie, metaboliese asidose of die wat gelyktydig kaliumsparende diuretika (bv. spironolaktoon, eplerenoon, triamtereen, of amiloried), kaliumaanvullings of kaliumbevattende soutvervangers gebruik, veral by pasiënte met ingekorte nierfunksie, kan dit lei tot beduidende toename in serumkalium. Hiperkalemie kan ernstige, soms noodlottige disritmieë veroorsaak (sien afdeling 4.5 en afdeling 4.3).

Diabetiese pasiënte

By diabetiese pasiënte wat met orale antidiabetiese middels of insulien behandel word, moet glukemiese kontrole sorgvuldig gemonitor word gedurende die eerste maand van behandeling met RAN-PERINDOPRIL 4 (sien afdeling 4.5).

Dubbele blokkade van die renien-angiotensien-aldosteroon sisteem (RAAS)

Daar is bewys dat die gelyktydige gebruik van AOE-remmers, angiotensien-II reseptor blokkeerders (ARBs) of aliskiren die risiko van hipotensie, hiperkalemie kan verhoog, en nierfunksie verlaag (insluitende akute nierversaking). Dubbele blokkade van RAAS deur die gelyktydige gebruik van RAN-PERINDOPRIL 4 en aliskiren is daarom teenaangedui (sien afdeling 4.3).

RAN-PERINDOPRIL 4 moet nie gelyktydig met aliskiren gebruik word nie (sien afdeling 4.3).

Die kombinasie van perindopril met sakubitriel/valsartan is teenaangedui as gevolg van die verhoogde risiko van angio-edeem (sien afdeling 4.3). Sakubitriel/valsartan moet nie geïnisieer word tot 36 uur na die laaste dosis van perindopril-terapie geneem is nie. As behandeling met sakubitriel/valsartan gestaak word, moet perindopril-terapie nie binne 36 uur na die laaste dosis van sakubitriel/valsartan geïnisieer word nie (sien afdelings 4.3 en 4.5).

Gelyktydige gebruik van ander NEP-inhibeerders (bv. rasekadotriel) en AOE-remmers kan ook die risiko van angio-edeem verhoog (sien afdeling 4.5). 'n Deeglike voordeel-risiko bepaling is daarom nodig voordat behandeling met NEP-inhibeerders (bv. rasekadotriel) geïnisieer word by pasiënte op perindopril.

Gelyktydige gebruik van mTOR-inhibeerders (bv. sirolimus, everolimus, temsirolimus:

Pasiënte wat gelyktydig mTOR-inhibeerders (bv. sirolimus, everolimus, temsirolimus) terapie gebruik, kan 'n verhoogde risiko van angio-edeem hê (bv. swelling van die lugweë of tong, met of sonder respiratoriese inkorting (sien afdeling 4.3).

Litium

Die kombinasie van litium en RAN-PERINDOPRIL 4 word oor die algemeen nie aanbeveel nie (sien afdeling 4.5).

Kaliumsparende diuretika, kaliumaanvullers of kalium-bevattende soutsubstitute:

Die kombinasie van RAN-PERINDOPRIL 4 en kaliumsparende diuretika, kaliumaanvullers of kaliumbevattende soutsubstitute word oor die algemeen nie aanbeveel nie (sien afdeling 4.5).

Primêre aldosteronisme:

Pasiënte met primêre hiperaldosteronisme sal oor die algemeen nie op anti-hipertensiewe medikasie deur inhibisie van die renien-angiotensienstelsel respondeer nie. Die gebruik van RAN-PERINDOPRIL 4 word daarom nie aanbeveel nie.

Gelyktydige gebruik van fluorokinolone:

Gelyktydige gebruik van fluorokinolone en RAN-PERINDOPRIL 4 kan akute nierskade (AK) by pasiënte presipiteer, veral die met matige tot ernstige nierversaking en bejaarde pasiënte (sien afdeling 4.3). Nierfunksie moet beraam word voordat behandeling geïnisieer word en gemonitor word tydens

behandeling, met gelyktydige gebruik van fluorokinolone en RAN-PERINDOPRIL 4 (sien afdelings 4.3 en 4.5).

Onaktiewe bestanddele

Pasiënte met seldsame oorerflike probleme van galaktose onverdraagsaamheid, totale laktase tekort of glukose-galaktose wanabsorpsie moet nie hierdie medisyne neem nie.

4.5 Interaksie met ander medisyne en ander vorme van interaksie

Medisyne wat hiperkalemie induseer

Sommige medisyne of terapeutiese klasse mag die voorkoms van hiperkalemie verhoog: kaliumsoute, kaliumsparende diuretika, AOE-remmers, angiotensien-II-reseptorantagoniste, NSAIGMs, hepariene, immuunonderdrukkende middels soos siklosporien of takrolimus, trimetoprim. Die kombinasie van hierdie medisyne verhoog die risiko van hiperkalemie.

Gelyktydige gebruik teenaangedui (sien afdeling 4.3)

Dubbele blokkade van die RAAS met ARBs, AOE-remmers of aliskiren:

Kliniese proefdata het aangedui dat dubbele blokkade van die renien-angiotensien-aldosteroonstelsel (RAAS) deur die gesamentlike gebruik van AOE-remmers, angiotensien-II reseptorblokkeerders of aliskiren geassosieer word met ‘n hoër voorkoms van ongunstige effekte soos hipotensie, hiperkalemie en verlaagde nierfunksie (sien afdeling 4.3, en afdeling 4.4).

Estramustien

Risiko van verhoogde ongunstige effekte soos angio-edeem.

Kaliumsparende diuretika (bv. triamtereen, amiloried), kaliumsoute

Hiperkalemie (potensieel noodlottig), veral tesame met nierinkorting (toegevoegde hiperkalemiese effekte).

Litium

Verhogings in serum litiumkonsentrasies en toksisiteit is aangemeld tydens gelyktydige toediening van litium met AOE-remmers soos RAN-PERINDOPRIL 4**.** Gebruik van RAN-PERINDOPRIL 4 met litium is teenaangedui (sien afdeling 4.3).

Aliskiren

By diabetiese of nierinkortingspasiënte, risiko van hiperkalemie, verslegting van nierfunksie en kardiovaskulêre morbiditeits- en mortaliteitstoename.

By pasiënte, anders as diabetiese of ingekorte nierfunksie pasiënte, kan die risiko van hiperkalemie, verslegting van nierfunksie en kardiovaskulêre morbiditeit en mortaliteit toeneem.

Ekstrakorporeale behandelings

Ekstrakorporeale behandelings wat lei tot kontak van bloed met negatief-gelaaide oppervlakke soos dialise of hemofiltrasie met sekere hoë-vloeimembrane (bv. poliakrilonitrielmembrane) en lae digtheid lipoproteïenaferese met dekstraansulfaat as gevolg van verhoogde risiko van ernstige anafilktoïede reaksies (sien afdeling 4.3). As sulke behandelings nodig is, moet oorweging daaraan geskenk word om ‘n ander tipe dialisemembraan of ‘n ander klas van antihipertensiewe middel te gebruik.

Sakubitriel/Valsartan

Die gelyktydige gebruik van perindopril met sacubitril/valsartan is teenaangedui aangesien die gelyktydige inhibisie van neprilisien en AOE die risiko van angio-edeem kan verhoog. Sakubitriel/valsartan moet nie tot 36 uur na die laaste dosis van perindopril-terapie begin word nie. Perindopril-terapie moet nie tot 36 uur na die laaste dosis van sakubitriel/valsartan begin word nie (sien afdelings 4.4 en 4.3)

Fluorokinolone en AOE-remmers/Renien-angiotensien reseptorblokkeerders

Gelyktydige gebruik van fluorokinolone en RAN-PERINDOPRIL 4 kan akute nierskade presipiteer (sien afdelings 4.3 en 4.4). Daar is aangemeld dat AKI voorgekom het kort nadat siprofloksasien aan pasiënte voorgeskryf is wat enalapril geneem het. Die interaksie tussen AOE-remmers en fluorokinolone om AKI te presipiteer is ‘n klaseffek vir alle AOE-remmers en nie slegs enalapril nie en ook ‘n klaseffek van alle fluorokinolone, nie slegs met siprofloksasien nie.

Gelyktydige terapie met AOE-remmer en angiotensien-reseptorblokkeerder

Daar is in literatuur aangemeld dat by pasiënte met bevestigde aterosklerotiese siekte, hartversaking, of met diabetes met eindorgaanskade, gelyktydige terapie met AOE-remmer en angiotensien-reseptor-blokkeerder geassosieer word met ‘n hoër voorkoms van hipotensie, sinkopee, hiperkalemie, en verergering van nierfunksie (insluitende akute nierversaking) vergeleke met die gebruik van ‘n enkele renien-angiotensien-aldosteroon- stelselmiddel. Dubbele blokkade (bv, deur ‘n AOE-remmer met ‘n angiotensien-II-reseptor antagonis te kombineer) moet beperk word tot individuele gedefinieerde gevalle met noukeurige monitering van nierfunksie, kaliumvlakke, en bloeddruk.

Ko-trimoksasool (trimetoprim/sulfametoksasool)

Pasiënte wat ko-trimoksasool (trimetoprim/ sulfametoksasool) gelyktydig neem, kan ‘n verhoogde risiko vir hiperkalemie hê (sien afdeling 4.3).

Gelyktydige gebruik wat spesiale voorsorg nodig het

Antidiabetiese middels (insuliene, orale hipoglukemiese middels)

Epidemiologiese studies het aangedui dat gelyktydige toediening van AOE-remmers en antidiabetiese medisyne (insuliene, orale hipoglukemiese middels) ‘n verhoogde bloedglukose verlagende effek kan veroorsaak met ‘n risiko van hipoglukemie. Dit kom voor asof hierdie verskynsel meer waarskynlik gedurende die eerste weke van gesamentlike behandeling en by pasiënte met nierinkorting voorkom.

Baklofen

Verhoogde antihipertensiewe effek. Moniteer bloeddruk en pas die antihipertensiewe dosering aan indien nodig.

Nie-kaliumsparende diuretika

Pasiënte op diuretika, en veral die wat volume- en/of souttekort het, kan oormatige afname in bloeddruk na aanvang van terapie met RAN-PERINDOPRIL 4 ervaar. Die moontlikheid van hipotensiewe effekte kan verminder word deur onttrekking van die diuretikum, deur verhoging van die soutinname voordat met terapie met lae en progressiewe dosisse van RAN-PERINDOPRIL 4 begin word.

By arteriële hipertensie, wanneer vorige diuretiese terapie sout/volume-uitputting kon veroorsaak het, moet die diuretikum gestaak word voordat met RAN-PERINDOPRIL 4 begin word**,** in watter geval ‘n nie-kaliumsparende diuretikum daarna weer toegevoeg word of daar moet met RAN-PERINDOPRIL 4 begin word teen ‘n lae dosering en geleidelik verhoog word.

By diureties-behandelde kongestiewe hartversaking, moet met RAN-PERINDOPRIL 4 teen ‘n baie lae dosis begin word, moontlik na verlaging van die dosis van die geassosieerde nie-kaliumsparende diuretikum.

In alle gevalle, moet nierfunksie (kreatinienvlakke) gemonitor word gedurende die eerste paar weke van RAN-PERINDOPRIL 4**-**terapie.

Kaliumsparende diuretka (eplerenoon, spironolaktoon)

Met eplerenoon of spironolaktoon teen dosisse tussen 12,5 mg tot 50 mg per dag en met lae dosisse van AOE-remmers:

In die behandeling van klas II-IV hartversaking (NYHA) met 'n uitwerpingsfraksie < 40 %, en voorheen behandeling met AOE-iremmers en lusdiuretika, is daar 'n risiko van hiperkalemie, potensieel dodelik, veral in geval van nie-nakoming van die voorskrifaanbevelings met hierdie kombinasie.

Voordat hierdie kombinasie geïnisieer word, kontroleer vir die afwesigheid van hiperkalemie en nierinkorting.

Noukeurige monitering van die kalium en kreatinien word aanbeveel in die eerste maand van die behandeling, een keer 'n week aan die begin en dan maandeliks daarna.

Nie-steroïdale anti-inflammatoriese geneesmiddels (NSAIGMs) insluitende aspirien ≥ 3 g/dag

Wanneer RAN-PERINDOPRIL 4 gelyktydig met nie-steroïdale anti-inflammatoriese geneesmiddels toegedien word is (bv. asetielsalisielsuur teen anti-inflammatoriese doseringsregimens, COX-2-inhibeerders en nie-selektiewe NSAIGMs), kan versterking van die antihipertensiewe effek voorkom. Gesamentlike gebruik van RAN-PERINDOPRIL 4 en NSAIGMs kan lei tot verhoogde risiko van verswakkende nierfunksie, insluitende moontlike akute nierversaking, en 'n verhoging in serumkalium, veral by pasiënte met swak voorafbestaande nierfunksie. Die kombinasie moet veral by bejaardes met versigtigheid toegedien word. Pasiënte moet voldoende gehidreer wees en oorweging moet daaraan geskenk word om die nierfunksie te monitor na inisiëring van gesamentlike terapie, en periodiek daarna.

Rasekadotriel

AOE-remmers (bv. perindopril) is bekend om angio-edeem te veroorsaak. Hierdie risiko kan verhoog word wanneer gelyktydig met rasekadotriel ('n medisyne wat gebruik word teen akute diaree) gebruik word.

mTOR-inhibeerders (bv. sirolimus, everolimus, temsirolimus)

Pasiënte wat mTOR-inhibeerders gelyktydig gebruik kan 'n verhoogde risiko hê vir angio-edeem (sien afdeling 4.4).

Gelyktydige gebruik wat spesiale voorsorg nodig het

Antihipertensiewe medisyne en vasodilatore

Gelyktydige gebruik van hierdie medisyne kan die hipotensiewe effekte van RAN-PERINDOPRIL 4 verhoog**.** Gelyktydige gebruik met nitrogliserien en ander nitrate, of ander vasodilatore, kan bloeddruk verder verlaag.

Gliptiene (saksagliptien, vildagliptien)

Verhoogde risiko van angio-edeem, as gevolg van dipeptidielpeptidase IV (DPP-IV) verlaagde aktiwiteit deur die gliptien, by pasiënte wat ook met 'n AOE-remmers soos RAN-PERINDOPRIL 4 behandel word**.**

Trisikliese antidepressante/antipsigotika/anestetika

Gelyktydige gebruik van sekere narkosemiddels, trisikliese antidepressante en antipsigotika met AOE-remmers soos RAN-PERINDOPRIL 4 kan tot verdere verlaging van bloeddruk lei (sien afdeling 4.4).

Asetielsalisielsuur, trombolitika, beta-blokeerders en nitrate

RAN-PERINDOPRIL 4 kan gelyktydig met asetielsalisielsuur (wanneer as trombolitikum gebruik word), trombolitika, beta-blokkeerders en/of nitrate gebruik word.

Simpatomimetika

Simpatomimetika kan antihipertensiewe effekte van RAN-PERINDOPRIL 4 verminder.

Goud

Nitritoïedreaksies (simptome sluit in gloede in gesig, naarheid, braking en hipotensie) word minder dikwels aangemeld by pasiënte op terapie met inspuitbare goud (natriumaurotiomalaat) en gelyktydige AOE-remmer-terapie, insluitende RAN-PERINDOPRIL 4**.**

4.6 Fertiliteit, swangerskap en laktasie

Swangerskap

Die gebruik van RAN-PERINDOPRIL 4 is teenaangedui tydens swangerskap. Swanger vrouens moet ingelig word oor die moontlike gevare vir die fetus en moet nie RAN-PERINDOPRIL 4 tydens swangerskap neem nie (sien afdeling 4.3). Pasiënte wat swangerskap beplan, moet oorgeskakel word na alternatiewe anti-hipertensiewe behandelings wat 'n bewese veiligheidsprofiel het vir gebruik tydens swangerskap. Wanneer swangerskap gediagnoseer word, moet behandeling met RAN-PERINDOPRIL 4 onmiddellik gestaak word en indien toepaslik, moet met alternatiewe terapie begin word.

Daar is aangemeld dat fetale blootstelling aan AOE-remmers tydens die eerste trimester van swangerskap geassosieer word met verhoogde risiko van wanvorming van die kardiovaskulêre (atriële en/of ventrikulêre septale defek, pulmonêre stenose, patent ductus arteriosus) en sentrale senuweestelsel (mikrokefalie spina bifida) en van nierwanvormings.

RAN-PERINDOPRIL 4 kruis die plasenta en dit kan aangeneem word dat dit versteuring in fetale bloeddruk regulatoriese meganismes veroorsaak.

Oligohidramnios asook hipotensie, oligurie en anurie in pasgeborenes, is aangemeld na toediening van RAN-PERINDOPRIL 4 gedurende die tweede en derde trimester. Gevalle van defektiewe skedelossifikasie is waargeneem. Prematuriteit en lae geboortemassa kan voorkom (sien afdeling 4.3). Suigelinge wat *in utero* blootgestel is aan RAN-PERINDOPRIL 4 moet noukeurig gemonitor word. Peritoneale dialise kan van geringe voordeel wees in die verwydering van RAN-PERINDOPRIL 4 vanuit die neonatale sirkulasie.

Borsvoeding

Veiligheid by laktasie is nie vasgestel nie (sien afdeling 4.3).

4.7 Effekte op die vermoë om te bestuur en masjinerie te gebruik

RAN-PERINDOPRIL 4 het geen direkte invloed op die vermoë om te bestuur en masjinerie te gebruik nie, maar individuele reaksies wat verwant is aan lae bloeddruk kan by sommige pasiënte voorkom, veral met die aanvang van behandeling of in kombinasie met ‘n ander antihipertensiewe middel. Die vermoë om te bestuur of masjinerie te gebruik kan gevolglik benadeel word.

4.8 Ongunstige effekte

Getabulleerde lys van ongunstige reaksies

MedDRA stelsel orgaanklas	**Frekwensie**	**Ongewenste reaksies**
Bloed- en limfatiese stelsel versteurings	Minder dikwels	Afnames in hemoglobien en hematokrit, trombositopenie, leukopenie/neutropenie, agranulositose of pansitopenie, eosinofilie, hemolitiese anemie.
Immuunsteselversteurings	Minder dikwels	Angio-edeem van die gesig, ekstremiteite, lippe, slymvliesmembrane, tong, glottis en/of larinks.
Metabolisme en voedingsvertseurings	Minder dikwels	Hiperkalemie, hiponatremie, hipoglukemie.
Psigiatriese versteurings	Minder dikwels	Gemoedsversteurings, slaapversteuring.
Senuweestelselversteurings	Dikwels	Duiseligheid, hoofpyn, parestesie, vertigo.

	Minder dikwels	Slaperigheid, sinkopee, verwarring.
Oogversteurings	Dikwels	Visuele versteurings.
Oor- en labirintversteurings	Dikwels	Tinnitus.
Kardiale versteurings	Minder dikwels	Palpitasies, tagikardie, angina pectoris, disritmie, miokardiale infarksie (sien afdeling 4.4).
Vakculêre versteurings	Dikwels	Hipotensie.
	Minder dikwels	Vaskulitis, beroerte moontlik sekondêr tot uitermatige hipotensie by hoë-risiko pasiënte (sien afdeling 4.4).
Respiratoriese, torakale en mediastinale versteurings	Dikwels	Hoes, dispnee.
	Minder dikwels	Brongospasma, rinitis, eosinofiliese pneumonie.
Gastroïntestinale versteurings	Dikwels	Diaree, abdominale pyn, hardlywigheid, disgeusie, dispepsie, naarheid, braking.
	Minder dikwels	Droë mond, pankreatitis.
Hepatobiliêre versteurings	Minder dikwels	Hepatitis, of sitolities of cholestaties.
Vel- en subkutane weefselversteurings	Dikwels	Pruritus, uitslag.
	Minder dikwels	Urtikarie, fotosensitiwiteitsreaksies, pemfigoïed, hiperhidrose, veelvuldige eriteem; psoriase verergering.
Muskuloskeletale en bindweefselversteurings	Dikwels	Spierkrampe.
	Minder dikwels	Artralgie, mialgie.
Renale en urinêre versteurings	Minder dikwels	Nierontoereikendheid, akute nierversaking.
Voortplantingstelsel- en borsversteurings	Minder dikwels	Erektiele wanfunksie.
Algemene versteurings en toedienplektoestande	Dikwels	Astenie.
	Minder dikwels	Borskaspyn, malaise, perifere edeem,

		pireksie, sweet.
Ondersoeke	Minder dikwels	Verhoogde bloedureum, verhoogde bloed-kreatinien, verhoogde bloedbilirubien, verhoogde lewerensieme.
Besering, vergiftiging en komplikasies rakende prosedure	Minder dikwels	Val.

Aanmelding van vermoedelike ongunstige reaksies

Aanmelding van vermoedelike ongunstige reaksies na goedkeuring van die medisyne is belangrik. Dit verseker voortgesette monitering van die voordeel/risiko balans van die medisyne. Gesondheidsorgvoorsieners word versoek om enige vermoedelike ongunstige reaksies aan SAHPRA aan te meld *via* die "**6.04 Adverse Drug Reactions Reporting Form**", wat aanlyn beskikbaar is onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8.

4.9 Oordosis

Sien afdeling 4.8.

Simptome van oordosis

Ernstige hipotensie, elektrolietversteurings en nierversaking.

Behandeling van oordosis

Behandeling is simptomaties en ondersteunend. Geaktiveerde houtskool kan in ernstige oordosering gegee word as die pasiënt binne 1 uur van inname aanmeld. Behandeling bestaan uit volume toenname om hipotensie te korrigeer en dehidrasie te behandel en elektrolietwanbalanse. RAN-PERINDOPRIL 4 is deur hemodialise verwyderbaar.

5. FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

Klas & Kategorie: A 7.1.3 Ander hipotensiewe middels

Perindopril inhibeer angiotensien-I-omsettingsensiem (AOE) aktiwiteit. Dit inhibeer die omsetting van die relatief onaktiewe angiotensien-I na die aktiewe angiotensien-II. Angiotensien-II is 'n kragtige

vasokonstriktor en stimuleer die vrystelling van aldosteroon. Verminderde angiotensien-II vlakke het ‘n daling in vasopressor aktiwiteit en ‘n afname in aldosteroon sekresie, met moontlike klein stygings in serumkalium, tot gevolg.

Daar word ook gedink dat AOE-inhibisie afbraak van bradikinien kan inhibeer wat tot verhoogde bradikinienvlakke kan lei.

Perindopril werk deur sy aktiewe metaboliet, perindoprilaat. Die ander metaboliete toon geen inhibisie van AOE-aktiwiteit *in vitro* nie.

‘n Afname in die sistoliese en diastoliese bloeddruk beide in die rugliggende en staande posisies is waargeneem. Die antihipertensiewe aktiwiteit is maksimaal tussen 4 en 6 uur na ‘n enkeldosis en word volgehou vir ten minste 24 uur.

In terme van die trog *versus* piek bloeddruk effek, wissel die trogeffek tussen 75 - 100 % van die piekeffekte.

5.2 Farmakokinetiese eienskappe

Absorpsie

Perindopril word goed geabsorbeer na orale toediening (piekkonsentrasie binne 1 uur) met groot tussen-pasiënt veranderlikheid. Die plasma halflewe van perindopril is gelyk aan 1 uur.

Die biobeskikbaarheid van perindoprilaat, die aktiewe metaboliet, is 27 %.

Die tyd om piek-serumvlak van perindoprilaat, die aktiewe metaboliet, te behaal, is binne 3 tot 4 uur en piek-farmakologiese aktiwiteit word binne 4 tot 6 uur behaal.

Die inname van voedsel verminder omsetting na perindoprilaat, en dus biobeskikbaarheid. Perindopril moet daarom oraal toegedien word as ‘n enkel daaglikse dosis in die oggend voor ontbyt.

Verspreiding

Die volume van verspreiding is ongeveer 0,2 L/kg vir ongebonde perindoprilaat. Proteïenbinding is gering (binding van perindoprilaat aan plasmaproteïene is 20 %, hoofsaaklik aan angiotensien-omskakelingsensiem), maar is konsentrasie-afhanklik.

Biotransformasie

Afgesien van die aktief perindoprilaat, lei perindopril tot 5 ander metaboliete, waarvan almal onaktief is.

Uitskeiding

Perindoprilaat word in die urine uitgeskei en die terminale half-leeftyd van die ongebonde gedeelte is ongeveer 17 uur, met gelykstaat binne 4 dae tot gevolg.

Eliminasie van perindoprilaat is stadiger by bejaardes, en ook in pasiënte met hart- of nierversaking. By sulke pasiënte moet dosisaanpassing gemaak word in verhouding tot die mate van vermindering in kreatinienopruiming.

Dialise-opruiming van perindoprilaat is gelyk aan 70 mL/min.

Perindopril kinetika word gemodifiseer in pasiënte met sirrose: hepatiese opruiming van die moederverbinding word met die helfte verminder. Die hoeveelheid van perindoprilaat wat egter gevorm word, word nie verminder nie en daarom is dosisaanpassing nie nodig nie.

6. FARMASEUTIESE BESONDERHEDE

6.1 Lys van onaktiewe bestanddele

- Anhidriese kolloïdale silika
- Laktosemonohidraat
- Magnesiumstearaat
- Mikrokristallyne sellulose

6.2 Onverenigbaarhede

Nie van toepassing nie.

6.3 Rakleeftyd

36 maande.

6.4 Spesiale voorsorgmaatreëls vir bewaring

Bewaar by of benede 25 °C in die oorspronklike verpakking, beskerm teen vog.

6.5 Aard en inhoud van die verpakking

Kartonne bevat 30 tablette verpak in kouevorm stulpstroke van 10 tablette elk. Kouevorm stulpstroke bestaan uit kouevorm stulplaminaat bestaande uit aluminiumfoelie (een kant blink, saggetemper, helder; dowwe kant lakgelamineer aan geörienteerde poliamiedfilm; helder kant lakgelamineer aan

PVC-film) PVC en poliamied met 'n rugkant van aluminiumfoelie bedek met hitte seëllak aan die binnekant.

Alternatiewelik word 10 tablette verpak in PVC-stulpstroke in 'n driedubbele gelamineerde aluminiumsakkie bestaande uit helder PVC-film met 'n rugkant van aluminiumfoelie bedek met hitte seëllak aan die binnekant. Drie sulke PVC-stulpstroke word verder in 'n driedubbele gelamineerde aluminiumsakkie met 'n droogmiddel verpak en verseël.

7. HOUER VAN DIE REGISTRASIESERTIFIKAAT

Ranbaxy Pharmaceuticals (Pty) Ltd

Lautreweg 14

Stormill, Uitbreiding 1, Roodepoort

Johannesburg,

1724.

8. REGISTRASIENOMMER:

42/7.1.3/0107

9. DATUM VAN DIE EERSTE GOEDKEURING/HERNUWING VAN DIE GOEDKEURING

18 April 2008

10. DATUM VAN HERSIENING VAN DIE TEKS

25 February 2022

Botswana: S2 Reg. nr.: BOT0101268

Namibië: NS2 Reg. nr.: 20/7.1.3/0348