**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*

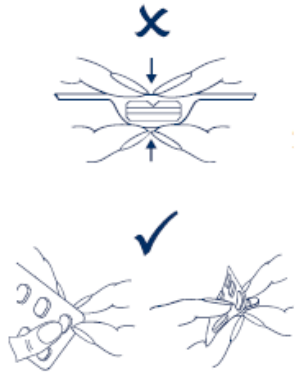
No dosage adjustment is necessary in patients with hepatic impairment.

**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**

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|---|
| 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 class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| *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

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|---|
| Botswana: S2 Reg. no.: BOT0101268 |
| Namibia: NS2 Reg. no.: 20/7.1.3/0348 |