

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Perindopril Krka 8 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg perindopril tert-butylamine, equivalent to 6.676 mg perindopril.

Excipient(s) with known effect:

Each tablet contains 120.8 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Tablets are white to almost white, round (diameter 12 mm), slightly biconvex, one side scored tablets with bevelled edges. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension:

Treatment of hypertension.

Stable coronary artery disease:

Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

4.2 Posology and method of administration

Posology

The dose should be individualised according to the patient profile (see section 4.4) and blood pressure response.

Hypertension:

Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy (see sections 4.3, 4.4, 4.5 and 5.1).

The recommended starting dose is 4 mg given once daily in the morning.

Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.

After one month of treatment, the daily dose may be increased to 8 mg once daily.

Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics.

Caution is therefore recommended since these patients may be volume and/or salt depleted.

If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with perindopril (see section 4.4).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).

Stable coronary artery disease:

Perindopril 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 and provided that the 4 mg dose is well tolerated.

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 1 "Dosage adjustment in renal impairment"). The dose should be increased only if the previous lower dose is well tolerated.

Patients with renal impairment

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in Table 1 below:

Table 1: Dosage adjustment in renal impairment.

| Creatinine clearance (ml/min) | Recommended dose |
|---|-----------------------------|
| $Cl_{Cr} \geq 60$ | 4 mg/day |
| $30 < Cl_{Cr} < 60$ | 2 mg/day |
| $15 < Cl_{Cr} < 30$ | 2 mg every other day |
| Haemodialysed patients*, $Cl_{Cr} < 15$ | 2 mg on the day of dialysis |

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

Patients with hepatic impairment

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Perindopril Krka in children and adolescents aged below 18 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made. Therefore, use in children and adolescents is not recommended.

Method of administration

Oral use

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

4.3 Contraindications

- Hypersensitivity to the active substance, to any other ACE inhibitor or to any of the excipients listed in section 6.1;
- History of angioedema associated with previous ACE inhibitor therapy (see section 4.4);
- Hereditary or idiopathic angioedema;
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- The concomitant use of Perindopril Krka with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment ($GFR < 60 \text{ ml/min/1.73 m}^2$) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Perindopril Krka must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5);
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4).

4.4 Special warnings and precautions for use

Stable coronary artery disease:

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

Hypotension:

ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely 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 sections 4.5 and 4.8). 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 (see 4.2 and 4.8). 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 sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Aortic and mitral valve stenosis, hypertrophic cardiomyopathy:

As with other ACE inhibitors, perindopril should be given with caution in patients with mitral valve stenosis or obstruction of the outflow tract of the left ventricle (such as aortic stenosis or hypertrophic cardiomyopathy).

Renal impairment:

In cases of renal impairment (creatinine clearance <60 ml/min) the initial perindopril dosage should be adjusted according to the creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of serum potassium and creatinine are part of normal medical practice for these patients (see section 4.8).

In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually 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. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril 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 perindopril may be required.

Haemodialysis patients:

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

Kidney transplantation:

There is no experience regarding the administration of perindopril 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 rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, perindopril should promptly be discontinued, and appropriate monitoring should be initiated and continued until the complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been found useful in relieving these symptoms.

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

adrenaline and/or the maintenance of a patent airway. The patient should be kept 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 an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of perindopril. Treatment with perindopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, 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.

Anaphylactoid reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. with *Hymenoptera* venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but, they reappear upon inadvertent re-challenge.

Hepatic impairment:

Rarely, 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 ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor 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. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril 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. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and the 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. As with other ACE inhibitors, perindopril 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. 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 agents that produce hypotension, perindopril 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.

Serum potassium:

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), uncontrolled diabetes mellitus intercurrent events, in particular dehydration, acute cardiac decompensation and metabolic acidosis; or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers).

Hyperkalemia can cause serious, sometimes fatal arrhythmias. Potassium-sparing diuretics angiotensin-receptor blockers and the above mentioned agents should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

Diabetic patients:

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

Lithium:

The combination of lithium and perindopril is generally not recommended (see section 4.5).

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

The combination of perindopril 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 drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

Lactose:

Perindopril Krka tablets contain lactose (as lactose monohydrate). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6)

4.5 Interaction with other medicinal products and other forms of interactions

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 (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Drugs inducing hyperkalaemia

Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim, co-trimoxazole (trimethoprim/sulfamethoxazole). The combination of these drugs increases the risk of hyperkalaemia.

Concomitant use contra-indicated (see section 4.3):

Aliskiren:

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

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use not recommended (see section 4.4):Aliskiren:

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

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.

Estramustine:

Risk of increased adverse effects such as angioneurotic oedema (angioedema).

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

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

Although serum potassium usually remains within normal limits, hyperkalaemia (potentially lethal) may occur in some patients treated with perindopril especially in conjunction with renal impairment (additive hyperkalaemic effects). Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when perindopril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of perindopril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

For use of spironolactone in heart failure, see below.

Lithium:

Reversible increases in serum lithium concentration and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination therapy proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Concomitant use which requires special care:Antidiabetic agents (insulins, oral hypoglycaemic agents):

Epidemiological studies have suggested that the concomitant administration of ACE inhibitors and antidiabetic medicines (insulin, 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 an ACE inhibitor. 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 perindopril.

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

In diuretic-treated congestive heart failure, the ACE inhibitor 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 ACE inhibitor 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.

A close monitoring of the kalaemia and creatinaemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid \geq 3 g/day:

When ACE-inhibitors are 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 ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Medicines increasing the risk of angioedema

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Concomitant use which requires some care:

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Gliptins (linagliptin, saxagliptin, sitagliptin, 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.

Tricyclic antidepressants / antipsychotics / anaesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Gold:

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.) Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Breastfeeding Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

There was no effect on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines

Perindopril krka has no or negligible 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 medication.

As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

a. Summary of safety profile

The safety profile of perindopril is consistent with the safety profile of ACE inhibitors:

The most frequent adverse events reported in clinical trials and observed with perindopril are: dizziness, headache, paraesthesia, vertigo, visual disturbances, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, diarrhoea, dysgeusia, dyspepsia, nausea, vomiting, pruritus, rash, muscle cramps, and asthenia.

b. List of adverse reactions

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders:

Uncommon: eosinophilia

Very rare: decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia, haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4).

Metabolism and nutrition disorders:

Uncommon*: hypoglycaemia (see sections 4.4 and 4.5), hyperkalaemia, reversible on discontinuation (see section 4.4), hyponatraemia.

Psychiatric disorders:

Uncommon: mood disturbances, sleep disorder.

Nervous system disorders:

Common: headache, dizziness, vertigo, and paraesthesia

Uncommon*: somnolence, syncope

Very rare: confusion.

Eye disorders:

Common: visual disturbances.

Ear and labyrinth disorders:

Common: tinnitus.

Cardiac disorders:

Uncommon*: palpitations, tachycardia

Very rare: arrhythmia, angina pectoris (see section 4.4), myocardial infarction, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Vascular disorders:

Common: hypotension (and effects related to hypotension)

Uncommon*: vasculitis

Very rare: stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Unknown: Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea

Uncommon: bronchospasm

Very rare: eosinophilic pneumonia, rhinitis.

Gastrointestinal disorders:

Common: nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, and constipation

Uncommon: dry mouth

Very rare: pancreatitis.

Hepato-biliary disorders:

Very rare: hepatitis either cytolytic or cholestatic (see section 4.4).

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4)

Uncommon*: photosensitivity reactions, pemphigoid

Rare: psoriasis aggravation

Very rare: erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps

Uncommon*: arthralgia, myalgia.

Renal and urinary disorders:

Uncommon: renal insufficiency

Very rare: acute renal failure

Reproductive system and breast disorders:

Uncommon: erectile dysfunction

General disorders and administration site condition:

Common: asthenia

Uncommon*: chest pain, malaise, oedema peripheral, pyrexia.

Investigations:

Uncommon*: blood urea increased, blood creatinine increased

Rare: blood bilirubin increased, hepatic enzyme increased.

Injury, poisoning and procedural complications

Uncommon*: fall.

* Frequency calculated from clinical trials for adverse events detected from spontaneous report.

Cases of SIADH have been reported with other ACE inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE inhibitor therapy including perindopril.

Clinical trials:

During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3 %) of the 6122 perindopril patients and 12 (0.2 %) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0 % (n=366) versus 2.1 % (n=129) respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance

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4.9 Overdose

Symptoms

Limited data are available for overdose in humans. Symptoms associated with the overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

Management

The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindoprilat can be removed from the systemic circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for treatment-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, plain, ATC code: C09A A04

Mechanism of action

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme – ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (through inhibition of the negative feedback of renin release) and attenuated secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus activates the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

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

Pharmacodynamic effects

Hypertension

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressure in both supine and standing position is observed. Perindopril reduces peripheral vascular resistance, leading to systemic blood pressure reduction. As a consequence, peripheral blood flow increases with no effect on heart rate.

Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.

The antihypertensive activity is maximal between 4 and 6 hours after the single dose and is sustained for at least 24 hours; trough effects are about 87 % to 100 % of peak effect.

The decrease in blood pressure reduction occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves the large arteries elasticity and decreases the media/lumen ratio of small arteries.

An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic.

Clinical efficacy and safety

Patients with stable coronary artery disease

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90 % of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers. The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9 % (relative risk reduction of 20 %, 95 % CI [9.4; 28.6] – p<0.001).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2 % corresponding to a RRR of 22.4 % (95 % CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

Paediatric use:

The safety and efficacy of perindopril in children and adolescents aged below 18 years have not been established.

In an open, non-comparative clinical study in 62 hypertensive children aged from 2 to 15 years with a glomerular filtration rate > 30 ml/min/1.73 m², patients received perindopril with an average dose of 0.07 mg/kg. The dose was individualised according to the patient profile and blood pressure response up to a maximum dose of 0.135 mg/kg/day.

59 patients completed the period of three months, and 36 patients completed the extension period of the study, i.e. were followed at least 24 months (mean study duration: 44 months).

Systolic and diastolic blood pressure remained stable from the inclusion to the last assessment in patients previously treated by other antihypertensive treatments, and decreased in naïve patients.

More than 75% of children had systolic and diastolic blood pressure below the 95th percentile at their last assessment.

The safety was consistent with the known safety profile of perindopril.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Absorption and biotransformation

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a prodrug. 27 % of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As the ingestion of food decreases the conversion of perindopril to perindoprilat and hence bioavailability, perindopril should be taken orally as a single daily dose, before the morning meal.

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

Distribution

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20 %, principally to angiotensin converting, but is concentration-dependent.

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.

Elderly

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

Renal impairment

Dosage adjustment in renal insufficiency is advisable, depending on the degree of impairment (creatinine clearance).

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Hepatic impairment

Perindopril kinetics are modified in patient 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 (see sections 4.2 and 4.4).

5.3 Preclinical safety data

In the chronic oral toxicity studies conducted on rats and monkeys, the kidney was target organ with reversible damage.

No mutagenicity has been observed in *in vitro* or *in vivo* studies.

Reproduction toxicity studies (on rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity.

Nevertheless, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects in the late stage of foetal development. In rodents and rabbits, such effects result in foetal death and congenital abnormalities (renal lesions) as well as in increased peri- and postnatal mortality.

No carcinogenicity has been observed in long term studies conducted on rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium chloride hexahydrate
Lactose monohydrate
Crospovidone type A
Cellulose, microcrystalline
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture and light. Do not store above 30°C.

6.5 Nature and contents of container

Blister (OPA/Alu/PVC film, Alu foil): 10, 14, 28, 30, 50, 56, 60, 90 and 100 tablets in a box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Krka d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/041/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th August 2010
Date of last renewal: 26th April 2015

10 DATE OF REVISION OF THE TEXT

April 2020