SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide STADA 2 mg/0.625 mg Tablets
< Perindopril/Indapamide STADA 4 mg/1.25 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2 mg/0.625 mg Tablets
Each tablet contains 2 mg perindopril tert-butylamine salt, equivalent to 1.669 mg perindopril and 0.625 mg indapamide.

Excipient with known effect
Each tablet contains 58.47 mg of lactose monohydrate
4 mg/1.25 mg Tablets
Each tablet contains 4 mg perindopril tert-butylamine salt, equivalent to 3.338 mg perindopril and 1.25 mg indapamide

Excipient with known effect
Each tablet contains 58.47 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, rod shaped tablets having 'P' and 'I' engraved on either side of score line on one side and score line on the other side.
The tablet can be divided into equal doses.
White, rod shaped tablets having 'PI' debossed on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of essential hypertension for patients whose blood pressure is not adequately controlled on perindopril alone.

4.2 Posology and method of administration

Route of administration: Oral use

It is recommended that one Perindopril/Indapamide 2 mg/0.625 mg is taken daily, preferably in the morning before a meal. The dose should be adjusted according to the patient profile and blood pressure response. If blood pressure is not adequately controlled the dose may be increased to one Perindopril/Indapamide 4 mg/1.25 mg daily.

When clinically appropriate, direct change from monotherapy with perindopril to Perindopril/Indapamide may be considered. Individual dose titration with the components may be required.

Special populations

Elderly population (see section 4.4)
Treatment should be initiated at a dose of 2 mg/0.625 mg daily with consideration of the blood pressure response and renal function.

Renal impairment (see sections 4.3 and 4.4)
In severe renal failure, (creatinine clearance below 30 ml/min) treatment is contraindicated.

In patients with moderate renal impairment (creatinine clearance 30 to 60 ml/min), it is recommended to start treatment with the adequate dosage of the free combination. It is not necessary to change the dose when creatinine clearance is greater than or equal to 60 ml/min. Usual medical follow-up will include frequent monitoring of creatinine and potassium levels.

Hepatic impairment (see sections 4.3 and 4.4)
In severe hepatic impairment, treatment is contraindicated.
In patients with moderate hepatic impairment, no dose modification is required.

Paediatric population
Perindopril/Indapamide is not recommended for use in children and adolescents as the safety and efficacy of perindopril in children and adolescents, alone or in combination has not been established.

4.3 Contraindications

The use of Perindopril/Indapamide is contraindicated in patients with:
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Linked to perindopril
- hypersensitivity to any other ACE inhibitors
- history of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy
- hereditary/idiopathic angioedema
- second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- the concomitant use of Perindopril/Indapamide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1)
- Concomitant use with sacubitril/valsartan therapy. Perindopril/Indapamide must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

Linked to indapamide
- hypersensitivity to any other sulphonamides
- severe renal impairment (creatinine clearance below 30 ml/min)
- hepatic encephalopathy
- severe hepatic impairment
- hypokalaemia
- as a general rule, this medicine is inadvisable in combination with non-antiarrhythmic agents causing torsades de pointes (see section 4.5)
- lactation (see section 4.6)

Due to the lack of sufficient therapeutic experience, Perindopril/Indapamide should not be used in:
- dialysis patients
- patients with untreated decompensated heart failure

4.4 Special warnings and precautions for use

Special warnings
Common to perindopril and indapamide

Lithium
The combination of lithium and the combination of perindopril and indapamide is usually not recommended (see section 4.5).

Linked to perindopril

Risk of Neutropenia/ Agranulocytosis in Immuno-suppressed patients:
The risk of neutropenia appears to be dose and type-related and is dependent on patient's clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus, scleroderma and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor.

Strict compliance with the predetermined dose seems to be the best way to prevent the onset of these events.
However, if an angiotensin converting enzyme inhibitor is to be administered to this type of patient, the risk/benefit ratio should be evaluated carefully.

Hypersensitivity/angioedema (Quincke's oedema)
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. In such cases, treatment with perindopril should be stopped immediately and the patient should be monitored until the oedema has disappeared. In those instances where swelling was confined to the face and lips, the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
Angioedema associated with laryngeal oedema may be fatal. Involvement of the tongue, glottis or larynx may lead to an obstruction of the airways. A subcutaneous injection of adrenaline at 1:1,000 (0.3 ml to 0.5 ml) should be administered quickly and other appropriate measures taken.
The prescription of an angiotensin converting enzyme inhibitor should not subsequently be considered in these patients (see section 4.3).
Patients with a previous history of Quincke's oedema which was not linked to taking an angiotensin converting enzyme inhibitor have an increased risk of Quincke's oedema with an angiotensin converting enzyme inhibitor.

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.

Anaphylactic reactions during desensitisation
There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitisation treatment with hymenoptera (bees, wasps) venom. ACE inhibitors should be used with caution in allergic

patients treated with desensitisation, and avoided in those undergoing venom immunotherapy. However these reactions could be prevented by temporary withdrawal of ACE inhibitor for at least 24 hours before treatment in patients who require both ACE inhibitors and desensitisation.

Haemodialysis patients: Anaphylactoid reactions during membrane exposure
There have been reports of patients experiencing sustained life-threatening anaphylactoid reactions while receiving ACE inhibitors during dialysis with high flux membranes or low density lipoprotein apheresis with dextran sulphate adsorption. ACE inhibitors should be avoided in such patients. However, these reactions could be prevented by temporary withdrawal of ACE inhibitors for at least 24 hours before treatment in patients who require both ACE inhibitors and LDL apheresis.

Potassium-sparing diuretics, potassium salts
The combination of perindopril and potassium-sparing diuretics, potassium salts is usually not recommended (see section 4.5).

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 anti-hypertensive 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).

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.

<u>Linked to indapamide</u>
When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause hepatic encephalopathy. Administration of the diuretic-containing product, should be stopped immediately if this occurs.

Sultopride
The combination of indapamide and sultopride is usually not recommended (see section 4.5).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Special precautions for use

Linked to Perindopril/Indapamide

Renal impairment
In cases of severe renal impairment (creatinine clearance < 30 ml/min), treatment is contraindicated.
In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only. In these patients usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.
The drug is usually not recommended in case of bilateral renal artery stenosis or a single functioning kidney.

Hypotension and water and electrolyte depletion
There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore, systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhoea or vomiting.
Regular monitoring of plasma electrolytes should be carried out in such patients.

Marked hypotension may require the implementation of an intravenous infusion of isotonic saline.

Transient hypotension is not a contraindication to continuation of treatment. After re-establishment of a satisfactory blood volume and blood pressure, treatment can be started again either at a reduced dose or with only one of the constituents.

Potassium levels
The combination of perindopril and indapamide does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. As with any antihypertensive agent in combination with a diuretic, regular monitoring of plasma potassium levels should be carried out.

Linked to perindopril

Cough
A dry cough has been reported with the use of ACE inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If the prescription of an angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be considered.

Children
The efficacy and tolerability of perindopril in children and adolescents, alone or in a combination, have not been established.

Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion).

Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium-free diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites.

The blocking of this system with an angiotensin converting enzyme inhibitor may therefore cause, particularly at the time of the first administration and during the first two weeks of

treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, although rare, and with a variable time to onset.
In such cases, the treatment should then be initiated at a lower dose and increased progressively.

Elderly
Renal function and potassium levels should be tested before the start of the treatment. The initial dose is subsequently adjusted according to blood pressure response, especially in cases of water and electrolyte depletion, in order to avoid sudden onset of hypotension.

Patients with known atherosclerosis
The risk of hypotension exists in all patients but particular care should be taken in patients with ischaemic heart disease or cerebral circulatory insufficiency, with treatment being started at a low dose.

Renovascular hypertension
The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.
If Perindopril/Indapamide is prescribed to patients with known or suspected renal artery stenosis, treatment should be started in a hospital setting at a low dose and renal function and potassium levels should be monitored, since some patients have developed a functional renal insufficiency which was reversed when treatment was stopped.

Other populations at risk
In patients with severe cardiac insufficiency (grade IV) or in patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose. Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped: the ACE inhibitor should be added to the beta-blocker.

Anaemia
Anaemia has been observed in patients who have had a kidney transplant or have been undergoing dialysis. The reduction in haemoglobin levels is more apparent as initial values were high. This effect does not seem to be dose-dependent but may be linked to the mechanism of action of angiotensin converting enzyme inhibitors.
This reduction in haemoglobin is slight, occurs within 1 to 6 months, and then remains stable. It is reversible when treatment is stopped. Treatment can be continued with regular haematological testing.

Surgery
Angiotensin converting enzyme inhibitors can cause hypotension in cases of anaesthesia, especially when the anaesthetic administered is an agent with hypotensive potential.
It is therefore recommended that treatment with long-acting angiotensin converting enzyme inhibitors such as perindopril should be discontinued where possible one day before surgery.

Aortic stenosis / hypertrophic cardiomyopathy
ACE inhibitors should be used with caution in patients with an obstruction in the outflow of the left ventricle.

Hepatic failure
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).

Serum potassium
ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalaemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

Linked to indapamide

Water and electrolyte balance

Sodium levels
These should be tested before treatment is started, then at regular intervals. All diuretic treatment can cause a reduction in sodium levels, which may have serious consequences. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients (see sections 4.8 and 4.9).

Plasma potassium
Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. The risk of onset of lowered potassium levels (< 3.4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure.

In such cases hypokalaemia increases the cardiac toxicity of cardiac glycosides and the risk of rhythm disorders.

Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe rhythm disorders, in particular torsades de pointes, which may be fatal.

In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment.

Detection of hypokalaemia requires its correction. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

Plasma magnesium
Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8).

Calcium levels
Thiazide diuretics and thiazide-related diuretics may reduce urinary excretion of calcium and cause a mild and transient increase in plasma calcium levels. Markedly raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases the treatment should be stopped before investigating the parathyroid function.

Blood glucose
Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

Uric acid
Tendency to gout attacks may be increased in hyperuricaemic patients.

Renal function and diuretics
Thiazide diuretics and thiazide-related diuretics are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25 mg/l, i.e. 220 µmol/l for an adult).

In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient, according to the Cockroft formula:

cl_{cr} = (140 - age) x body weight / 0.814 x plasma creatinine level

with: age expressed in years
body weight in kg
plasma creatinine level in micromol/l

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

Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.

Athletes
Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

Excipients
contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Linked to Perindopril/Indapamide

Combinations which are not recommended

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of perindopril combined with indapamide with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Combinations which require special care

Baclofen
Concomitant treatment of anti-hypertensives with baclofen is likely to cause increased hypotension; the dosage of Perindopril/Indapamide should be adjusted accordingly and close monitoring of blood pressure and renal function is recommended.

Non-steroidal anti-inflammatory medicinal products (including acetylsalicylic acid at high doses): the administration of a non-steroidal anti-inflammatory medicinal product may reduce the diuretic, natriuretic and antihypertensive effects in some patients. In elderly patients and patients who may be dehydrated there is a risk of acute renal failure, therefore monitoring of renal function at the initiation of treatment is recommended. Patients should be well hydrated.

Combinations, which require some care

Imipramine-like antidepressants (tricyclics), neuroleptics
Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Corticosteroids, tetracosactide
Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

Other antihypertensive agents: use of other antihypertensive medicinal products with perindopril/indapamide could result in additional blood pressure lowering effect.

Linked to perindopril

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).

Combinations which are contraindicated

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

Combinations which are not recommended

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. 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.

Medicines increasing the risk of angioedema: Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Combinations which require special care

Antidiabetic agents (insulin, hypoglycaemic sulphonamides): Reported with captopril and enalapril.
The use of angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting

reduction in insulin requirements).

Combinations which require some care

Anaesthetic drugs
ACE inhibitors may enhance the hypotensive effects of certain anaesthetic drugs. Therefore the combination of perindopril/indapamide should be avoided during this time.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide
Concomitant administration with ACE inhibitors may lead to an increased risk of leucopenia.

Diuretics (thiazide or loop diuretics): Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypotension when initiating therapy with 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.
Linked to indapamide

Combinations which are not recommended

Sultopride: Increased risk of ventricular arrhythmia, especially torsades de pointes (hypokalaemia favours the occurrence of this adverse event) (see section 4.4).

Combinations which require special care

Torsades de pointes inducing drugs : Due to the risk of hypokalaemia, indapamide should be administered with caution when associated with medicinal products that induced torsades de pointes such as class IA antiarrhythmic agents (quinidine, hydroquinidine, disopyramide); class III antiarrhythmic agents (amiodarone, dofetilide, ibutilide, bretylium, sotalol); some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.

Potassium-lowering drugs: amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), Tetracosactide, stimulant laxatives:
Increased risk of low potassium levels (additive effect).

Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides. Non-stimulant laxatives should be used.

Digitalis preparations: Hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digitalis. Monitoring of plasma potassium, magnesium and ECG is recommended and, if necessary, adjusting the treatment.

Combinations, which require some care

Metformin
Metformin can cause possible renal impairment which in effect can lead to lactic acidosis. Linked to diuretics and in particular to loop diuretics.
Do not use Metformin when plasma creatinine levels exceed 15 mg/l (135 micromol/l) in men and 12 mg/l (100 micromol/l) in women.

Iodinated contrast media
In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.

Calcium (salts)
Risk of increased levels of calcium due to reduced elimination of calcium in the urine.

Ciclosporin
Risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no salt and water depletion.

4.6 Fertility, pregnancy and lactation

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

Pregnancy
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).

As indapamide is a chlorosulphamoyl diuretic its administration to pregnant women must be avoided. Diuretics should never be given as treatment for physiological oedema of pregnancy (which does therefore not require treatment). Exposure to thiazide diuretics during the third trimester can lead to reduction of maternal plasma volume and uteroplacental blood flow, which may cause foeto-placental ischemia, with a risk of impaired fetal growth.

Moreover, rare cases of hypoglycaemia and thrombocytopenia in neonates have been reported following exposure near term.

Breast-feeding
Because no information is available regarding the use of perindopril during breast-feeding, it is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
Indapamide is contraindicated during lactation. Indapamide is excreted in human milk. Thiazide diuretics have been associated, during breast-feeding, with decrease or even suppression of lactation. Hypersensitivity to sulfonamide-derived drugs, hypokalaemia and nuclear icterus might occur.
As serious adverse reactions might occur in breast-fed infants, a decision should be made whether to discontinue breast-feeding or to discontinue therapy taking account the importance of this therapy for the mother.

4.7 Effects on ability to drive and use machines

Perindopril/Indapamide has minor or moderate influence on the ability to drive and use machines. Neither of the two active substances affects alertness but individual reactions related to low blood pressure may occur in some patients, particularly at the start of the treatment or in combination with another antihypertensive medication. As a result, the ability to drive or operate machines may be impaired.

4.8 Undesirable effects

Summary of the safety profile
The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide. Approximately four percent of the patients on treatment with Perindopril/Indapamide may experience hypokalaemia (potassium level < 3.4 mmol/l).

The most commonly reported adverse reactions with indapamide are hypokalaemia, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

Tabulated list of adverse reactions
The following undesirable effects have been observed during treatment with perindopril/indapamide and ranked under the following frequency:
Very common (> 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Endocrine disorders
Rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and nutrition disorder
Common: Hypokalaemia (see section 4.4)
Uncommon: Hyponatraemia (see section 4.4)
Rare: Hypochloraemia
Hypomagnesaemia

Psychiatric disorders
Uncommon: Depression.

Vascular disorders
Uncommon: Hypotension whether orthostatic or not.
Rare: Flushing.
Not known: Raynaud's phenomenon.

Blood and lymphatic system disorders
Very rare: Thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.
Anaemia (see section 4.4) has been reported with angiotensin converting enzyme inhibitors in specific circumstances (patients who have had kidney transplants, patients undergoing haemodialysis).

Nervous system disorders
Uncommon: Headache, asthenia, feelings of dizziness, mood disturbance and/or sleep disturbances, paraesthesia.

Eye disorders
Not known: Choroidal effusion, acute myopia, acute angle-closure glaucoma

Respiratory, thoracic and mediastinal disorders

Common: Dry cough has been reported with the use of angiotensin converting enzyme inhibitors.

Gastrointestinal disorders
Common: Constipation, dry mouth, nausea, epigastric pain, anorexia, abdominal pains, taste disturbance.
Very rare: Pancreatitis, in the case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see sections 4.3 and 4.4).

Skin and subcutaneous tissue disorders
Uncommon: Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic asthmatic reactions.
Maculopapular eruptions, purpura, possible aggravation of pre-existing acute disseminated lupus erythematosus.

Skin rash
Rare: Psoriasis aggravation.
Very rare: Angioedema (Quincke's oedema) (see section 4.4).

Musculoskeletal and connective tissue disorders
Uncommon: Cramps.

Renal and urinary disorders
Rare: Acute renal failure, anuria / oliguria.

Reproductive system and breast disorders
Uncommon: Erectile dysfunction.

Investigations
- Increase in uric acid levels and in blood glucose levels during treatment.
- Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped. This increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.
- Increased levels of potassium, usually transitory.

Rare: Raised plasma calcium levels.

Description of selected adverse reactions
During phase II and III studies comparing indapamide 1.5 mg and 2.5 mg, plasma potassium analysis showed a dose-dependent effect of indapamide:
- Indapamide 1.5 mg: Plasma potassium < 3.4 mmol/l was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.
- Indapamide 2.5 mg: Plasma potassium < 3.4 mmol/l was seen in 25 % of patients and < 3.2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.

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 the national reporting system listed in Appendix V.

4.9 Overdose

The most common adverse event in the case of an overdose is hypotension. This can be linked to the following:

Nausea, vomiting, cramps, sleepiness, mental confusion, oliguria which could progress to anuria (due to hypovolaemia), electrolyte imbalance (low sodium and potassium levels).

The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal.

If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an IV infusion of isotonic saline may be given, or any other method of volaemic expansion may be used.
Perindoprilat, the active form of perindopril, can be dialysed (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor and Diuretic
ATC code: C09BA04

Perindopril/Indapamide is a combination of perindopril tert-butylamine salt and indapamide to treat essential hypertension in patients whose blood pressure is not adequately controlled by perindopril alone. Perindopril tert-butylamine salt is an angiotensin converting enzyme inhibitor. Indapamide is a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.

Pharmacological mechanism of action
Perindopril/Indapamide produces an added synergy of the antihypertensive effects of the two components.

Linked to perindopril
Perindopril is an inhibitor of the angiotensin converting enzyme (ACE inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; in addition the enzyme stimulates the secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides.

This results in:
- a reduction in aldosterone secretion,
- an increase in plasma rennin activity, since aldosterone no longer exercises negative feedback,
- a reduction in total peripheral resistance with a preferential action on the vascular bed in muscle and the kidney, with no accompanying salt and water retention or reflex tachycardia, with chronic treatment.

The antihypertensive action of perindopril also occurs in patients with low or normal renin concentrations.
Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive.

Perindopril reduces the work of the heart:
- by a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins: reduction in pre-load,
- by reduction of the total peripheral resistance: reduction in afterload.

Studies carried out on patients with cardiac insufficiency have shown:
- a reduction in left and right ventricular filling pressures,
- a reduction in total peripheral vascular resistance,

- an increase in cardiac output and an improvement in the cardiac index,
- an increase in regional blood flow in muscle.

Exercise test results also showed improvement.

Linked to indapamide

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the re-absorption of sodium in the cortical dilution segment. It increases urine output and in effect increases excretion of sodium and chloride and to a lesser extent, the excretion of potassium and magnesium, so having an antihypertensive action.

Characteristics of antihypertensive action

Linked to Perindopril/Indapamide

In hypertensive patients regardless of age, Perindopril/Indapamide exert a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing. This antihypertensive effect lasts for 24 hours. The reduction in blood pressure is obtained in less than one month without tachyphylaxis; stopping treatment has no rebound effect. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the products administered alone.

Linked to perindopril

Perindopril is active in all grades of hypertension: mild to severe. A reduction in systolic and diastolic arterial pressure has been observed in the lying and standing position.
The antihypertensive activity after a single dose is at its maximum between 4 and 6 hours and remains consistent during the course of 24 hours.
At 24 hours, there is a high degree of residual blocking of angiotensin converting enzyme (80 %).

In patients who respond well to treatment, blood pressure is stabilised after one month without any signs of tachyphylaxis.

Withdrawal of treatment has no rebound effect on hypertension.

Perindopril has vasodilator properties and restores elasticity of the main arterial trunks, corrects histomorphometric changes in resistance arteries and produces a reduction in left ventricular hypertrophy.

If necessary, the addition of a thiazide diuretic leads to an additive synergy.

The combination of an angiotensin converting enzyme inhibitor with a thiazide diuretic decreases the hypokalaemia risk associated with the diuretic alone.

Linked to indapamide

Indapamide, as monotherapy, has an antihypertensive effect, which lasts for 24 hours, this effect occurs at doses at which the diuretic properties are minimal. Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance.

Indapamide reduces left ventricular hypertrophy.

When a dose of thiazide diuretic and thiazide-related diuretics is exceeded, the antihypertensive effect reaches a plateau, whereas the adverse effects continue to increase. If the treatment is ineffective, the dose should not be increased.

Furthermore, it has been shown that regardless of the duration of treatment in hypertensive

patients, indapamide:
- Has no effect on lipid metabolism: triglyceride, LDL-cholesterol and HDL-cholesterol.
- Has no effect on carbohydrate metabolism, even in diabetic hypertensive patients.

Linked to 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

Linked to Perindopril/Indapamide
There is no significant difference between the pharmacokinetic characteristics of perindopril and indapamide co-administered and those obtained from perindopril and indapamide administered separately.

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

Perindopril is a prodrug. Twenty seven percent 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 ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

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

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 enzyme, but is concentration-dependent.

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 decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (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 (see sections 4.2 and 4.4).

Indapamide
Absorption
Indapamide is absorbed from the digestive tract rapidly and completely.

The peak plasma level reached in humans is approximately one hour after oral administration of the product. Plasma protein binding is 79 %.

Elimination
The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70 % of the dose) and faeces (22 %) in the form of inactive metabolites.

Special population
Renal insufficiency
The pharmacokinetics of patients with renal failure is unaffected.

5.3 Preclinical safety data

Perindopril and indapamide in combination has slightly increased toxicity than that of its components.
Renal manifestations do not seem to be potentiated in rats. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seem to be increased in the rat (compared to perindopril alone).

Nonetheless, these adverse effects are shown at dose levels giving a very marked safety margin in comparison to the therapeutic doses used.
Preclinical studies performed separately with perindopril and indapamide did not show genotoxic, carcinogenic or teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica hydrophobic colloidal Cellulose, microcrystalline
Lactose monohydrate
Magnesium Stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years
2 months after first opening the laminated pouch containing the blister strip of tablets

6.4 Special precautions for storage

For 2mg and 4mg: PVC / PVdC – Aluminium blisters: Store in the original package to protect from moisture.
When unopened, this medicinal product does not require any special temperature storage conditions.
Once the laminated pouch is opened, blister strips should be stored in the outer box below 30 °C.

For 4mg: Aluminium-Aluminium blisters: Store in the original package to protect from moisture. Store below 30°C

6.5 Nature and contents of container

For 2mg and 4mg: PVC / PVdC – Aluminium blisters: The tablets are packed in PVC / PVdC – Aluminium blisters within a protective aluminium pouch, including a desiccant protecting the tablets from moisture. The desiccant should not be swallowed.

For 4mg: Aluminium-Aluminium blisters:
The tablets are packed in Aluminium-Aluminium blisters packed in a carton.

Pack Sizes

30, 90 and 100

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2 – 18
61118 Bad Vilbel
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 106101 Perindopril/Indapamide STADA 2/0,625 mg, tabletten
RVG 106100 Perindopril/Indapamide STADA 4/1,25 mg, tabletten

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 4 juli 2011
Datum van laatste verlenging: 20 mei 2016

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 6.4 en 6.5: 30 juli 2024